Emotions and depression

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Emotions and depression are words that go together very naturally in ordinary language. It would be unexceptional to say that major depression is a disorder of the emotions. But while the definition of depression is operationalized and agreed, the definition of emotion has been, and is, surprisingly controversial. A recent review effectively suggested that it had come to mean anything one wants it to. The present volume certainly illustrates the pleomorphic character of the idea of emotion from infant development through neuroscience to psycho-pathology. It may be worth grounding the concept in its historical description and how I see it emerging in contemporary clinical controversies relevant to the treatment of depression.

In Western philosophical thought, it has been commonplace to oppose emotion and reason, and much argument about their respective value, primacy, and importance has followed. The science of emotion is a recent development. A convenient starting point to illustrate how the problem of understanding emotion can be framed is the well-known work of William James. In 1884, he addressed the question of where in the brain or body emotion should be located. The topographical representation of sensation and movement in different parts of the brain was newly recognized in the cerebral cortex. James wrote as follows:

My thesis...is that the bodily changes follow directly the perception of the exciting fact and that our feeling of the same changes...is the emotion. Common sense says we lose our fortune are sorry and weep, we see a bear, are frightened and run, we are incited by a rival, are angry and strike. The hypothesis here to be defended says that this order of sequence is incorrect....[T]he more rational statement is that we feel sorry because we cry, angry because we strike, afraid because we tremble and not that we cry, strike or tremble because we are sorry, angry or fearful as the case may be.

James was stating a hypothesis that runs highly counterintuitive to common understanding. However, most importantly, the question “what is emotion?” was now open to experiment and such a theory was open to falsification. Science was taking over from philosophy. It soon became clear that emotional responses were represented in the brain and James’ theory was partly refuted by experiments on deafferented or decerebrated animals by Cannon and Bard. The identification of emotional experience with specialized brain structures started with Cannon, and an association was made with the limbic circuit (originally proposed by Papez), including the hippocampus, the ipsilateral mammillary body, the anterior nucleus of the thalamus, the cingulate cortex, the parahippocampal gyrus, and the entorhinal cortex. The prefrontal cortex, septum, and amygdala are also now included in the so-called limi...
bic system. Modern neuroimaging has confirmed and extended our understanding of the functional connections of these structures, which show correlated activity at rest in the default-mode network and during emotional processing of various kinds. It is a useful hypothesis that emotion is an emergent property of synchronous activity in these brain areas. Neuroscience has thus affirmed and confirmed the engagement of the brain with the mind in relation to emotion. This has important, often forgotten, value in trying to understand the complex mental and physical presentations of mood disorder.

If the emotions were secondary to reason, as in "we lose our fortune are sorry and weep," then emotions become a simple function of mind. The tendency to divorce thinking and feeling from the body has been attractively phrased "Descartes' error" in the book of the same name by Antonio Damasio. Dualism is deeply embedded in our language and therefore in nonreflective thought. The very term mental illness immediately poses the problem. Can there be a disease of a brainless mind? How can one then imagine a physical treatment having value? Psychiatry has been deeply scarred by those of its practitioners who have insisted on a meaning for the mind necessarily separate from the body/brain. Damasio was influential in promoting the view that parts of the human brain are specialized for the representation, and therefore the experience, of emotion, and in a partial reinstatement of James' theories, via the somatic marker hypothesis (which will not be described in detail here). If some areas of the limbic cortex and related structures are ablated, then human beings become literally unable to experience emotion normally. This has a purely subjective dimension, but also a much more interesting consequence. This was long described informally as personality change. The original famous example, to which Damasio returned, was Phineas Gage, who sustained bilateral damage to his mesial frontal cortex when a tamping iron exploded through the front of his head in a railway construction accident. Gage's problem was described as a loss of his moral sense: he was "no longer Gage" in the words of contemporaries.

Modern neuroscience has clarified what impact ablation of the emotional sense actually has. It reduces the capacity of any individual to make decisions which involve value choices. The individual with a lesion of the mesial frontal cortex is cognitively intact: asked what they would do in simple morally valenced situations they will give a conventional correct reply. However, asked to make real decisions, it turns out they have lost the capacity to assess risk. They will make choices that promise large rewards, irrespective of whether they also carry a risk of large losses. They are apparently no longer able to balance prospective rewards and punishments. Risky choice is now seen to require emotional processes, if a person is to pursue adaptive strategies. The automatic emotional underpinning of human choice has spawned the new discipline of neuroeconomics.

The centrality of emotion in cognition frequently omits the discussion of pathological emotion. This is regrettable because psychiatric disorder usually represents experience on a continuum with normality. Its very extremes offer potential ways of testing hypotheses generated in mainstream normal psychology. This disjunction between the neuroscience of health and the traditions of psychiatry (and clinical psychology) has been unhelpful. Hence, we have been relatively slow to see neuroscience as offering key translational opportunities to understand and treat mental disorders better. This has now changed as several contributions in this volume will illustrate.

Nevertheless, clinical practice bears unmistakable scars from its past. In relation to the understanding of emotion and cognition in mood disorder, the most unhelpful factor has been the polarization between psychological and drug treatment.

The most influential contemporary psychological approach to mood disorder has been the cognitive theory originally developed by Beck in the 1970s, and relatively little modified since. Beck was exasperated by psychoanalysis and its passive acceptance of poor outcomes for patients in endless therapy. He listened to what patients told him about their conscious experience of depression and was struck by the distorted way in which they thought. He rejected the interpretations of the unconscious popular at the time and suggested instead that low mood is maintained by negative beliefs, thoughts, and reflections. He developed a therapy designed to reverse these conscious emotional biases. It involved both a Socratic critique of the patient’s faulty thinking and behavioral change.

Cognitive behavior therapy (CBT) has acquired very wide acceptance since. Unlike psychoanalysis, CBT lends itself to clinical trials, although the methodology of comparing the active treatment with a waiting-list control or “treatment as usual” is often poor, and together with publication bias has inflated estimates of its efficacy. Until quite recently, it has failed to engage with neuroscience.

For clinical psychologists, cognitive formulations have become pervasive. Abnormal beliefs or ways of thinking provide an explanation for why optimistic or depressive interpretations might arise when emotional events are experienced. This view of mood disorder and emotion lends itself to an exclusively mentalistic way of thinking. In other words, mental illness is thought of as not physical, just in the way that Descartes formulated the split between body and mind. Thus, although beliefs clearly are a product of brain function, any brain-based explanation drawing on cognitive formulations would be too complex to be of use in understanding mental disease. Because these formulations follow a folk psychology tradition, they receive easy acceptance from a general public who use Cartesian language in everyday life. More importantly, emotion fits easily into cognitive formulations and in a sense has been appropriated by mentalistic or “brainless” formulations of depression.
For psychiatrists, their most challenging patients are those for whom psychological treatment is not possible because, and honoring William James, the body is so evident in their presentations. There is the slowness of movement, thought, and action that characterizes the retardation of severe depression. This has always looked like an integrated impact of mood on the motor system. The arousal of anxiety argues for a similar overlap in brain representations of the autonomic nervous system and anxiety. Thus, the phenomena of severe depression argue for the potential power of brain abnormalities to condition experience through automatic rather than conscious cognitive mechanisms. If such effects have a substrate in those parts of the brain subserving emotional processing, then it is there that we should look for the actions of effective treatments. Electroconvulsive therapy, antidepressants, and ketamine have all been discovered largely by serendipity. Yet how they work has been the best clue we have to the neurobiology of mood disorder and its treatment. This relationship has motivated the whole field of psychopharmacology. It can provide models of drug action at the levels of receptor, cell, and brain system. Unfortunately, what the “mindless” formulations of psychopharmacology have traditionally left out is emotion. We should restore emotional experience to primacy, because we now appreciate that one effect of serotoninergic antidepressants is to blunt the emotions. This was first recognized in relation to sexual interest and performance. It is also seen in automatic processing of expressive faces. It suggests that some antidepressants may treat depression at the expense of normal emotion, while others like agomelatine may not.

What is important for the future is that the parallel paths to treatment provided by cognitive mechanisms on the one hand and biological on the other do not use mutually exclusive language and ideas. The neuroscience of the emotions can unite the mental and physical traditions in our understanding of mood disorder. The present volume will illustrate how this is happening.

References

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Les termes "émotion" et "dépression" vont très naturellement ensemble dans le langage ordinaire, et rien de plus banal que de dire que la dépression ma jeure est un trouble des émotions. Toutefois, alors que la définition de la dépression est standardisée et validée, celle de l’émotion a toujours été et, de façon surprenante, reste controversée. Une récente revue de la littérature a effectivement suggéré que ce terme en était venu à dire tout et n’importe quoi1. Le présent numéro de Medicographia illustre tout à fait la nature pléomorphe de l’idée d’émotion, que ce soit dans le contexte du développement du nourrisson, celui de la psychopathologie ou celui des neurosciences. Il peut donc être utile de définir le concept d’émotion dans le cadre de sa description historique, et d’observer comment il a surgi au milieu des controverses cliniques contemporaines concernant le traitement de la dépression.

La philosophie occidentale a fréquemment opposé l’émotion à la raison, et un grand nombre d’arguments sur la valeur, la prédominance et l’importance respectives de ces deux termes ont été avancés. La science de l’émotion est de développement récent. Les travaux bien connus de William James constituent un point de départ pratique pour illustrer comment le problème de la compréhension des émotions peut être délimité2. En 1884, alors que la représentation topographique des sensations et des mouvements dans différentes parties du cerveau venait d’être établie dans le cortex cérébral, cet auteur s’est demandé où, dans le cerveau ou dans l’organisme, les émotions étaient localisées. Citons William James :

« Selon mon hypothèse… les changements corporels sont directement consécutifs à la perception d’un stimulus et c’est notre sensation de ces mêmes changements… qui constitue l’émotion. Le sens commun nous fait dire que si nous perdons notre fortune nous sommes tristes et nous pleurons, si nous voyons un ours, nous sommes effrayés et nous nous mettons à courir, si nous sommes provoqués par un rival, nous sommes en colère et nous attaquons. L’hypothèse défendue ici considère que cet ordre séquentiel est incorrect… et qu’il est en fait plus rationnel de dire que nous nous sentons tristes parce que nous pleurons, en colère parce que nous attaquons, effrayés parce que nous tremblons et non que nous pleurons, attaquons ou tremblons parce que nous sommes respectivement tristes, en colère ou apeurés, selon le cas.

L’hypothèse énoncée par William James allait totalement à contre-courant du bon sens habituel. Mais l’essentiel était que la question « Qu’est-ce que l’émotion ? » était désormais ouverte à l’expérimentation et donc qu’une théorie de ce type pouvait être soumise à réfutation (au sens de Karl Popper). La science avait pris le pas sur la philosophie. Il est toutefois rapidement apparu que les réponses émotionnelles
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sur leur expérience consciente de la dépression, il fut frappé par leur manière déformée de penser. Il rejeta les interprétations relevant de l’inconscient ayant cours à l’époque, et avança au contraire que l’humeur dépressive était entretenue par des croyances, des pensées et des réflexions négatives. Pour inverser ces biais émotionnels conscients, il développa une modalité thérapeutique reposant sur une approche socratique des pensées erronées du patient et un changement comportemental. Cette thérapie comportementale et cognitive (TCC) a été largement acceptée depuis. Contrairement à la psychanalyse, la TCC peut se prêter à des études cliniques, bien que la méthodologie permettant de comparer le traitement actif à des contrôles placés sur une liste d’attente ou au “traitement habituel” soit souvent insuffisante. Ceci, et le fait que la TCC ait bénéficié de biais de publication, expliquent que l’efficacité de cette modalité thérapeutique ait été surestimée10. C’est pourquoi, jusqu’à une période très récente, la confrontation entre la TCC et les neurosciences n’a pas pu avoir lieu.

Pour les psychologues cliniciens, les formulations cognitives sont devenues omniprésentes. Des croyances ou des manières de pensées anormales fournissent une explication sur la raison pour laquelle des interprétations optimistes ou dépressives peuvent survenir lorsque des événements émotionnels sont vécus par le patient. Cette approche des troubles de l’humeur et de l’émotion favorise un mode de pensée de type exclusivement mentaliste. En d’autres termes, les maladies mentales sont considérées comme indépendantes du physique, exactement de la même manière que Descartes avait formulé la séparation entre le corps et l’esprit. Aussi, bien qu’il soit clair que les croyances sont un produit de la fonction cérébrale, toute explication basée sur le cerveau et invoquant des formulations cognitives serait trop complexe pour permettre de comprendre la maladie mentale. Dans la mesure où ces formulations sont le reflet de représentations psychologiques populaires dites « naives », elles sont facilement acceptées par le grand public, qui utilise un langage cartésien dans la vie quotidienne. Plus important encore, l’émotion se prête facilement aux formulations cognitives et, dans le cadre de la dépression, les formulations mentalistes ou « excluant le cerveau » se les sont pour ainsi dire appropriées.

Pour les psychiatres, les patients les plus difficiles à traiter sont ceux chez qui la psychothérapie n’est pas possible, car leur tableau clinique, (donnant ainsi raison à William James), contient de manière trop évidente une participation du corps, témoin la lenteur des mouvements, de la pensée et de l’action caractéristiques du ralentissement psychomoteur de la dépression. Ce phénomène a toujours été considéré comme un résultat d’un impact intégré de l’humeur sur le système moteur. La survenue d’une anxiété plaide pour un chevauchement similaire des représentations cérébrales du système nerveux autonome et de l’anxiété. Par conséquent, les phénomènes liés à la dépression sévère sont en faveur de la capacité potentielle des anomalies cérébrales à conditionner l’expérience par l’intermédiaire de mécanismes automatiques, plutôt que par des mécanismes cognitifs conscients. Si ces phénomènes ont pour origine les différentes zones du cerveau impliquées dans le traitement émotionnel, ce sont ces zones qu’il faut scruter à la recherche des actions des thérapeutiques médicamenteuses ou physiques déployées. Les effets des électrochocs, des antidépresseurs et de la kétamine ont été découverts largement par hasard. Et pourtant c’est bien leur mode d’action qui a fourni les meilleures pistes pour la compréhension de la neurobiologie des troubles de l’humeur et de leur traitement. C’est ce contexte qui a fait émerger et continue à inspirer le domaine de la psychopharmacologie grâce à laquelle sont fournis des modèles d’action médicamenteuse au niveau des récepteurs, des cellules et des systèmes cérébraux.

Il est malheureux que les formulations de la psychopharmacologie « excluant l’esprit » aient généralement comme effet d’éliminer… les émotions. C’est bien pourquoi il faut redonner à l’expérience émotionnelle toute son importance, car nous savons désormais que les antidépresseurs sérotoninergiques ont notamment comme effet d’émouvoir les émotions. Ce phénomène a été observé pour la première fois en relation avec la libido et les performances sexuelles11. Il a également été mis en évidence au cours du traitement neuronal automatique des visages expressifs ressentis comme menaçants12. Ceci suggère que certains antidépresseurs traitent la dépression aux dépens des émotions normales13, tandis que d’autres, comme l’agomélatine, sont libres d’effets de ce type.

Ce qui est essentiel pour l’avenir est que les thérapeutiques issues des voies parallèles que sont les mécanismes cognitifs d’une part et les mécanismes biologiques d’autre part évitent d’utiliser un langage et des idées mutuellement exclusifs. La neuroscience des émotions a ainsi vocation à unifier les approches mentaliste et physique de notre compréhension des troubles de l’humeur. Cette unification est en route, et c’est ce que ce numéro de Medicographia s’attache à démontrer.
Emotion and trauma

Without emotion, there can be no memory. An event needs to arouse neurological circuits that leave a memory potential “like a scar in brain tissue” (William James) or rather like a path carved out of the neuronal undergrowth. Everyday experience teaches us that what is a major event for one person may only be a minor incident for another. Thus trauma is defined not by the event in itself, but by its psychological impact. Memory is a heterogeneous system made up of neurology, affectivity, verbality, and cultural narratives. The biological component of emotion is physically determined by the functioning of a neuronal circuitry that mediates events and chemical compounds. Feeling is an emotion triggered by the representation of remembered images or individual and collective narratives. Healthy memory evolves, reworked over a lifetime, while traumatic memory stays fixed, but can be reworked employing targeted techniques.

A memory is said to be traumatic when a past event causing an emotional shock at the time is followed by a sustained aftershock of altered self-representation. Healthy memory is a heterogeneous system made up of neurobiology, interpersonal relationships, and collective narratives reworked over a lifetime. Traumatic memory, on the other hand, remains fixed on the recollection of misfortune and ceases to incorporate incoming self-representational data. Unable to rework the memory, the victim endures psychic agony as a prisoner of the past. Differing radically from an ordeal that a person confronts and overcomes before moving on, trauma fixes the mind on the memory of perpetually recurrent misfortune. Psychoanalysis likens traumatic memory to a break-in by a foreign body that plays havoc with the psychic apparatus. Neither internal conflict nor Oedipal neurosis, traumatic memory is the fear of death paralyzing the machinery of the mind.

Without emotion, there can be no memory. An event needs to arouse neurological circuits that leave a memory potential “like a scar in brain tissue” (William James) or rather like a path carved out of the neuronal undergrowth. Everyday experience teaches us that what is a major event for one person may only be a minor incident for another. Thus trauma is defined not by the event in itself, but by its psychological impact. This becomes easier to understand if we differentiate between emotion, caused by a cerebral stimulus or ingestion of a substance, and feeling, defined as emotion triggered by mental representation (a scenario made up of images and words).
Emotion

Emotion is regulated primarily by a neuronal substrate. The orbitofrontal cortex plays an important role in emotivity; with its connections to the amygdala and anterior cingulate cortex, it modulates the affective connotation of events. When prefrontal inhibition is impaired by disease or accident, the “unleashed” amygdala overstimulates the anterior cingulate limbic circuit. In such cases, the slightest event triggers uncontrollable emotion that spreads to the hypothalamus, midbrain, and brainstem nuclei: the motor expression of emotion becomes uncontrollable.5

Feeling

A child may be particularly given to emotion even when the affective component of its developmental niche is stable and well structured. Such emotivity is genetically determined, encoded in all mammals by a group of genes that undersynthesize a synaptic serotonin transporter protein.10 Fifteen percent of all mammals come into the world deprived of the natural emotional tranquility conferred by serotonin. If misfortune happens to strike, these 15% of minor serotonin transporters are seriously wounded. Faced by the slightest event, such children seek to downplay its emotional potential by self-centered behavior such as gaze aversion, rocking, twirling, and nail-biting. When emotion overwhelms them (as readily happens), it triggers autoaggressive behavior. Frightened by any relationship, they have never learned to direct toward others the interactive rituals that make for peaceful coexistence. The paradoxical result is that autoaggressive behavior has a tranquilizing effect.

Regardless of whether they are genetically hypersensitive or have amygdala hypertrophy induced by early deprivation, such children experience the frustration inevitably encountered in any game or conflictual situation as a source of violent stress. Any encounter triggers outward- and/or inward-directed aggression. Every emotional alert takes long to die down. Forever on standby, the hypothalamic-pituitary-adrenal axis increases mean circulating cortisol levels. The limbic cells that are supersensitive to cortisone swell in response, the ion channels open and let in potassium. The Na+/K+ gradient is reversed, causing such hyperosmolarity that the cell bursts. This process accounts for the limbic atrophy seen in depressed patients11 who progress from hypersensitivity to the slightest event to memory disturbance and affective indifference (Figure 3).12

Imprinting

During normal development, the same deprivation has different effects depending on when it occurs. It leaves its imprint on every human being who needs other people in order to complete his or her development. A sensory figure featuring at a sensitive moment in a child’s development becomes a key object that the child perceives over and above any other. From that point onwards a circuit is traced in its implicit memory, attaching the child to the familiar figure. Whether mother, father, peer, or place, this attachment figure makes the child feel secure and gives it the strength to explore its world with pleasure. Without such a figure, the child panics, runs in all directions, suffers emotional diarrhea, becomes accident-prone and is unable to process information correctly (Figure 4).13
Failed imprinting may be due as much to the child’s environment as to its development. A deprived niche (a dead or depressed mother, conjugal violence, or underprivilege) leaves no reassuring imprint in a child’s biological memory. Similarly, genetic disease causing a deficiency of acetylcholine, endogenous opioids or oxytocin undermines the biological basis for imprinting. Drugs may have the same effect: β-blockers, certain antidepressants and interferon (in 50% of prescriptions) make the body indifferent to contextual information.

Memory no longer retains an imprint once blunted emotion prevents an object or event from standing out in a child’s experience. In a world without emotion, everything is the same, there are no value judgments, no event is worth inscribing in memory, and no figure stands out for potential attachment.

Genetic determinants create a predisposition rather than determine an ineluctable fate. Minor serotonin transporters who live in a reassuring environment soon develop enough self-confidence and affective stability to begin exploring with pleasure. Conversely, major serotonin transporters living in longstanding isolation acquire an emotional vulnerability that subjects them to their impulses and the stimuli of others. This may account for the emotional storms in borderline states. Having suffered a torrent of early childhood traumas, the prefrontal lobes in such individuals fail to acquire the ability to inhibit emotion. Stimuli are too intermittent to develop the frontolimbic connections that could control the expression of emotion. A distorted interactional spiral then becomes established in which such children, who are incapable of controlling their impulses, sabotage the emotional reactions of those around them, thus jeopardizing their affective relationships with their attachment figures.

The insecurity of a child whose sensory niche has been deprived by parental misfortune (death, disease, marital breakdown, underprivilege) leads it to perceive its world as an unending series of alarms. The resulting prefrontal hypotrophy...
and limbic atrophy subject the child to its environmental stimuli since it is unable either to plan ahead or use its memory. Everything and anything frightens the child and triggers reactions of fight or flight.

**Erosion of the soul**

Once stress has been so overwhelming as to have consumed the capacity to respond, the physiological reactions of the burned-out amygdala induce a state of psychic numbness. An amygdala rendered dysfunctional by physiological burnout or head injury leads to anhedonia. Nothing excites such individuals anymore. They lose all taste for life.

Amygdala response is what determines whether an item of information is stored in memory. An alert amygdala ensures that some facts will become memory events. A numbed or lesioned amygdala, on the other hand, lets nothing through to memory. Thus the soldiers who took propranolol during the Iraq War in 1991 avoided the hypermesia of posttraumatic stress syndrome, but conversely experienced enormous gaps in memory.

Anhedonia—the inability to enjoy life—was described in the 19th century in melancholics, neurasthenics, and those with early dementia. The following variants were identified:

- Reactive anhedonia in subjects who once enjoyed life, but eventually experienced “erosion of the soul” after a trauma or cascade of painful events.
- Anhedonia as a personality trait reflecting a hyporeactive amygdala, in a subject whose life since childhood had been deprived, bleak, and led at slow pace in social isolation.

Prospective studies speak of “chronic depression” and psychotic tendencies. These traits are common among risk-takers who depend on strong stimuli to feel alive. Other instances include the astonishing anesthesias of psychotics capable of walking on a broken leg, remaining upright with peritonitis, or slicing into their forearms with no change in facial expression. Evidence suggests that such agenesia of the amygdala is due to the numbing of amygdala reactivity by opioid hypersecretion in response to early interactions in the first few months of life.

Victims of the prefrontal leukotomies practiced between 1935 and 1960 or patients with crude lobotomies caused by head injuries were found to have lost the ability to inhibit their behavioral or mental responses. Having lost the neurologic substrate required for the representation of time (memory and anticipation), such patients become incapable of imagining the effect that their words or acts could have (later) in the mind of someone else. Incapable of empathy, they give free rein to their impulses, as is seen after lobotomy, in frontotemporal dementia, sexual deviation, and in children under 4 who have yet to develop a theory of mind. As prisoners of the here and now, incapable of combining representation of the past with that of the future, they are unable to give meaning to what they perceive. They become detached from an existence that no longer holds meaning for them, switching between overreaction and indifference, depending on the stimuli emanating from those around them. When people are busy around them, they can become agitated; but when things calm down again, they become immobile, bereft of either internal language or emotion.

**Empathy**

Patients whose amygdala has been destroyed by lobotomy become totally indifferent. If you ask them to lay their hand on the table and you then pretend to strike it with a hammer, they do not even flinch, since they do not anticipate feeling pain. They remain stone-faced and devoid of empathy in front of any manifestation of pain or suffering in another person. Yet paradoxically they can be hurt by their own indifference of affection. Lobotomized patients often say: “I miss the time when I felt pain and suffering. I at least felt alive.” Does this mean that pain and suffering are part of the human condition and that they help us develop the empathy that enables everyone to live together? The minor frustrations that are inevitable in daily life (e.g., a delayed feed or temporary absence of its mother for an infant, a physical malaise or a relationship issue) cause minor levels of discomfort or distress that train us in empathy. Child survivors of natural disasters, war, or serious illness show an astonishing acceleration of emotional maturity.

Affective anesthesia thus has a variety of causes:

- **Dysfunctional frontolimbic circuitry due to early deprivation of environmental stimuli leading to amygdala burnout.**
- **Erosion of the soul caused by a cascade of insidious trauma such as underprivilege or an unwelcoming environment (soul-destroying work, harassment, racism).**
- **Ingestion of amygdala-numbing substances such as propranolol, β-blockers, or certain psychotropic agents.**
- **Lobotomy due to head injury.**

Recent neuroimaging data confirm the time-honored neurologic concept of the complementarity of opposites between pleasure and pain. Dopaminergic and opioid systems preferentially stimulate the ventral segmental area of the brainstem. But excessive stimulation of the inferior longitudinal fasciculus (pleasure area) eventually stimulates the lateral spinothalamic fasciculus (pain area), and vice versa. We see this pair of opposites at work in attachment behavior: an infant moves away from its secure attachment figure and explores its environment until it experiences fright, at which point it scuttles back to huddle deliciously close to its mother. An infant that experiences neither fright nor frustration is numbed by the absence of stimuli and neither mentalizes nor develops an attachment figure. Perhaps, when poets write that magic consists of transforming pain by endowing it with inordinate nobility (“nothing makes us greater than great pain… the most beautiful songs are the most despairing”) they are simply giving voice to this combination of contrary emotions.
Emotion and trauma – Cyrulnik

Reworking emotion

It is thus possible to rework the pain in a feeling by ennobling it or transforming it into poetry. In doing so we become author-actors in the representation of our life stories.26

The memory of a psychologically traumatic syndrome is constraining and painful: an image of terror takes over our thoughts, seeps into our mental lives, and constantly recurs, haunting us in particular in nightmares (Figure 5). The memory of a terrifying event is said to ease over time, but it is more accurate to say that time gives the “victim” an opportunity to develop the relationships that will help rework the memory so that he or she is no longer its victim. Emotion is transformed by meeting someone with whom one can share a narrative. Words have to be found in which to address the person we trust.

Healthy memory adjusts its representation of the past to current circumstances: 73 14-year-old boys answered a 28-point questionnaire describing how they perceived their current situation: “Is religion helpful to you?”, “What do you enjoy most?”, “Is the discipline you receive upsetting to you?” Thirty-four years later, the investigators recontacted 67 of the ex-adolescents, now aged 48, and re-asked the same questions: the answers were astonishingly different. Twenty-eight percent of the 14-year-olds had replied that they “enjoyed school and homework least”; this figure jumped to 58% at age 48. One adolescent in four considered that he enjoyed peer relationships most, a proportion that expanded to one in two of the 48-year-olds. Eight adolescents in ten (82%) were upset by the corporal punishment they received, whereas at age 48 the upset was remembered by only about a third (28%).27 The emotion we experience at the time is different from the emotion we remember. It is in the present that we become drunk on the Baudelaire’s “wine of memory” and the reconstituted past. Reworking of the emotion associated with memory is thus the general rule. Predictably, the memory associated with the least reworked emotion is the memory of horror.

Three factors combine to keep a memory intact and accurate or allow it to fade into haziness:

◆ Time of occurrence of the traumatizing experience. Pre-verbal terror leaves a trace in biological memory, but no memory. The persons concerned do not know why they have been made sensitive to this type of event: they have source amnesia. Later in life, they may become able to find images and/or words to represent the source event or situation that has given the particular taste to their world, but it will not necessarily be factually accurate (false allegations of rape, impressions of persecution, mistaken identity). If terror strikes when a person is depressed or has been made vulnerable by previous trauma, there is a high probability of the image of the terrifying event becoming part of a psychologically traumatic syndrome, comprising a fascination with the aggressor who is recalled in hyper-real focus, while the setting in which the aggression occurred remains hazy.28

◆ The emotion of horror. We do not need to experience horror in order to strengthen our memory of horrific images. People only have to be shown one series of horrific images and another of attractive images. A month later, they clearly remember the horrific images, but retain only vague recollections of the attractive photographs.29 Horror has a fascination that fixes memory, whereas pleasure has a relaxing effect that traces in memory a readiness for well-being that is devoid of individual images.30

◆ The power of words. The words that accompany photographs have a strongly reworking effect on memory. When horrific photographs are shown with an accompanying commentary that gives meaning to the horror involved (the making of a hero, a noble sacrifice, or dramatic fiction), the horror of the memory will be largely blurred. But if attractive photographs are shown with an uplifting commentary, the attractive memory becomes clearer.

Even written words are involved in the reworking of memory. When the written words trawl a painful past for the details of an atrocity in order to commit them to paper, the mental work required can concentrate the mind to a degree approximating to psychological trauma syndrome. Primo Levi dwelled on Auschwitz to the point of suicide, while Jorge Semprún described his drafts on his experience of Buchenwald as having bled for 20 years. Conversely, when “victims” write on trauma to give others the pleasure of understanding or to create a work of art (novel, film, art, or poetry), they rework the representation of what they have suffered.31 In restoring the past by “the wine of remembrance,” collective narratives play a ma-

Figure 5. Memory of a psychologically traumatic syndrome.

Images of a terrifying event tend to become pervasive within the subject’s mental life, whereas the precise memory of the traumatic event tends to fade.

Man aiming gun. © Micha Klootwijk/123RF.
When traumatized parents are sustained by the cultural narratives that surround them, they give their children the impression of emerging victorious. But when the cultural context isolates, aggresses, or despises them, the unresolved trauma suffered by the parents destabilizes the children.

References

Keywords: affective relationships; cultural narratives; neurological circuits; sensory deprivation

Émotions et traumatismes

Sans émotion, pas de mémoire. Il faut un événement pour éveiller les circuits neurologiques qui tracent dans le cerveau une aptitude mnésique, « comme une cicatrice dans le tissu cérébral » (William James) ou plutôt comme, le « frayage » « d’un chemin dans la brousse des neurones. Dans la vie quotidienne, on constate que, ce qui est un événement majeur pour l’un, n’est qu’un incident mineur pour l’autre. Ce qui fait trauma ce n’est donc pas le réel de l’accident, c’est l’effet psychique qu’il produit. Le phénomène mnésique est un système hétérogène, composé de neurologie, d’affectivité, de verbalité et de récits culturels. La composante biologique de l’émotion est matériellement déterminée par le fonctionnement neuronal courtisé par les événements et les substances. Le sentiment est une émotion provoquée par une représentation d’images mnésiques ou de récits individuels et collectifs. La mémoire saine évolutive se remanie avec l’histoire du sujet. La mémoire traumatique figée, peut intentionnellement être remaniée.
Biological sex differences begin in utero and continue to develop throughout life, based on biology and experience. The concept of gender requires disentangling biological (sex) and social (gender) constructs as well as considering the role that hormones and genes play in establishing emotional differences, especially those due to the sexual differentiation of the fetus and the reproductive cycle. Increasingly sophisticated functional neuroimaging techniques highlight what is known about brain sex differences, and its influence on different expressions of emotions. There is also limited evidence of difference in symptoms of depression between men and women, and conflicting reports about differential antidepressant response in men and women with major depressive disorder.

Since the mid-20th century, women have been viewed as the “expressive” experts and men the “instrumental” experts. Emotional competencies are so embedded in our popular notions of what it is to be female or male, that tests of gender role identification use emotion items as key components to identify a person as feminine and not masculine⁵ and there is a strong current of thinking that females have greater access to their emotions.⁶ However, while much of the popular imagination continues to maintain this divide between male and female emotions, the scientific literature has moved toward an understanding that there is a filigreed intertwining of biological, social, and interpretive dimensions that influences an individual’s emotional repertoire, leading to individual differences being greater than differences between sexes. These potential differences have implications when it comes to the etiopathology and treatment of psychiatric disorders, such as major depressive disorder (MDD), which include aberrant emotional function as a key component of the illness.

Sex and gender
“Sex” is indicative of the biological characteristics of the organism, while “gender” refers to the social situation of that phenotype—whether a person is interpreted by themselves and others as male or female. Gender operates at many levels—the personal, social, and institutional.⁶ One may have the biological characteristics of a male (XY), but want to be part of the gendered world of a female (XX). One’s gendered experience of being treated as male affects one’s biology to conform more closely to what is considered “maleness.” These experiences will shape neural circuits that will, in turn, mediate one’s actions and perceptions of the world.⁶
Sexual differentiation
The first step toward establishing sex differences occurs in the developing embryo. If the fetus is XY, there is a region on the short arm of the Y-chromosome, containing the gene SRY, that when switched on leads the indifferent gonad to develop into the testes. The testes begin to produce androgens in the sixth week of gestation and this has repercussions for each body system, including the nervous system. It is well understood from rodent studies that estrogen via testosterone synthesis early in development sets the neural circuitry in the XY brain on a course that differentiates it from female neural circuitry, especially in the areas of the brain that mediate sexual reproduction. Since the XX fetus does not have SRY, the indifferent gonad follows a developmental path toward becoming ovaries which do not secrete appreciable estrogen until much later in development and so with respect to brain development, the male brain sees testosterone and estrogen early and often, while the female brain develops essentially in their absence. The production of follicle-stimulating hormone (FSH) is thought to play a key role in the development of the ovaries. Both androgens and estrogens will affect neural circuits throughout life and are essentially growth factors causing dendrites and axons to grow as well as synapses and neural connections to form.

Hormonal and social effects on sex differences in emotion

♦ Hormones during reproductive cycle
The cyclic release of hormones in the ovarian cycle and the menstrual cycle has been viewed as sources of mood differences between females and males. It has not gone unnoticed that some neuropsychiatric disorders seem to be in synchrony with phases of the ovarian cycle and are so named: premenstrual dysphoric disorder (PMDD; low estrogen), catamenial epilepsy (high estrogen), and menstrual migraine (low estrogen). However, these conditions are very rare. While the prevalence of PMDD has been estimated to occur in 3% to 9% of the adult female population, a recent community study reported 1.3%. Since mood disorders are nearly twice as prevalent in females as in males, a discrepancy that begins at puberty and dissipates following menopause, it has been difficult to move away from hormonal explanations for women’s moods as opposed to men’s, with the late luteal or premenstrual phase perceived as a time of increased irritability and negativity, leading to the broader lay concept of premenstrual syndrome (PMS).

Attempts to correlate female gonadal hormones with women’s mood in both women with PMDD and women without disorders have been largely inconclusive. Studies on the effects of exogenous hormone administration on mood in menopausal women also reveal contradictory results; estrogen administration has been shown to reduce, increase, or have no significant effect on negative mood: “Studies conducted, however, have overwhelmingly refuted the presumption that gonadal steroid levels are abnormal in women with PMDD.” In studies of randomly recruited, non-help-seeking women, who were blinded to the purpose of the study, no correspondence was observed either between menstrual phase or ovarian steroids and either negative or positive mood. Rather it was psychosocial factors—stress and physical health—that were most highly correlated with mood (Figure 1). Thus, despite reports of a link between menstrual phase and self-reported mood, a direct relationship between ovarian hormones and mood is not well established (for review, see reference 20).

♦ Hormones and life changes during pregnancy and postpartum
Much has been written about the moods of women during pregnancy and delivery, especially with respect to depression and anxiety. The postpartum period is seen as a particularly vulnerable time for women, especially if there is prior depression or psychosis. What is not known is how much of postpartum mood depends on hormonal fluctuations and how much depends on the enormity of the undertaking of parenthood, societal expectations, and sleep deprivation. Robinson and Stewart suggest that the postpartum period is a time when family roles are reevaluated, often becoming more traditional with women taking on the greater load of household and childcare responsibilities. Changing roles and sleep deprivation may be strong drivers for mood shifts. These can be seen as affecting men as well; consequently, men may also be vulnerable to paternal postpartum depression, with rates ranging from 10.4%-25.6%. Thus, in the period when women most commonly suffer postpartum depression, significant numbers of men do as well. Since many studies show that children are affected by depression in fathers as well as mothers, this is an important, but as yet understudied aspect of men’s moods.

♦ Sex differences in “emotion behavior”
From a behavioral perspective, at least one approach has served to delineate emotions so the permutations and com-

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>CRESCEND</td>
<td>Clinical RESearch CENter for Depression</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DBS</td>
<td>deep brain stimulation</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>NCS</td>
<td>National Comorbidity Survey</td>
</tr>
<tr>
<td>PMDD</td>
<td>premenstrual dysphoric disorder</td>
</tr>
<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>vmPFC</td>
<td>ventromedial prefrontal cortex</td>
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</table>
Combinations can be viewed as “mixed and matched” by the sexes. 26,27 This framework addresses: (i) overt actions; (ii) subjective reports, and (iii) physiological responses. When emotion is deconstructed into these components, studies that only focus on sex differences do not account for the complexity of emotional processes. 28 With respect to overt actions, while men and women both report feeling sadness at the same levels, women tend to display overt signs of sadness while men tend to withdraw. However, this difference in behavioral repertoire may be situational, with women believing that they should verbally express their emotion while men do not. Both feel more expressive when talking with a woman.

In the case of alexithymia, a personality construct that is characterized by impoverished components of imagination, poor capacity for symbolic thought, and inability to experience and describe feelings, 29 neither subjective reports nor physiological response differs between the sexes. Numerous studies have failed to find a reliable sex difference. 30,31 In subjective reports, men and women report experiencing anger with equal intensity and frequency. 1 Physiological responses reveal that men tend to make evident more responses than women; however, with regard to fear, for example, there are no specific fear-related differences in autonomic response between females and males. 28

Figure 1. Linear mixed models of mood items with t-statistics of mood variables.
All models include measures of E1G, PdG, weekly social support, and subjective stress and physical health (*P<0.05, **P<0.01, ***P<0.0001). (A) Model of composite positive mood with E1G and PdG measured the same day. Composite positive mood is the average of happiness, confidence, enjoyment, energy, feeling of being on top of things, and motivation. Only perceived stress and physical health contributed significantly to the model (P<0.0001). (B) Model of composite negative mood with E1G and PdG measured the same day. Composite negative mood is the average of irritability, sadness, anxiety, and difficulty coping. Only perceived stress and physical health contributed significantly to the model (P<0.0001). (C) Model of irritability with E1G and PdG measured 1 day prior. PdG (P=0.0048), stress (P<0.0001), and physical health (P=0.0120) contributed significantly to the model.

Abbreviations: E1G, estrone glucuronide; PdG, pregnanediol-3 glucuronide.


Emotional regulation strategies vary with age in older women, but not so in men; use of acceptance did not decrease with age for women. Older men made the fewest reports of reappraisal, active coping, and acceptance. This suggests that men may find it harder than women to assume a positive, efficacious, or accepting attitude toward problems that arise in older age. Lack of acceptance, active coping, or reappraisal was not associated with depressive symptoms in the oldest age group as they were with the younger adults. 33 When taken together, these studies and others suggest that individual variation in emotion and its expression depend more on the
nature of the emotional stimulus, mental health status, context, age, and the response format. This complex pattern of findings is best accounted for by acknowledging that both society (gender) and biology (sex) are equal determinants of emotion: emphasizing sex differences in emotionality imposes a framework on the patient that might burden psychotherapy with stereotypes.

**Neural effects on sex differences in emotion**

How, and why, might emotions differ across sex? An “adaptationist perspective” affirms that the body’s individual organs serve several functions. Although there is an overlap in critical survival functions across sex, there are also important distinctions among several organ systems, namely, reproductive, endocrine, cardiovascular, digestive, and the central nervous system.

Three categories of drive are required for survival of any organism: homeostatic (maintaining key internal parameters in safe ranges), agonistic (self-preserving behaviors against hostile conspecifics or predators, and self-advancing behaviors against prey or rivals), and reproductive (finding suitable mates, birthing, nurturing, and defending young). For at least the latter two categories of drive, important differences exist between the males and females in nearly every species, including humans. These differences are reflected in the emotional circuitry of the brain, most notably in the so-called core limbic structures: the amygdala, hypothalamus, and hippocampus.

The emerging field of affective neuroscience has made rapid progress in delineating the neural substrates of emotion. The core limbic structures are essential for the generation of integrated emotional states such as fear, anger, or sadness. Other, more caudal, regions of the neouraxis, such as the brainstem, the periaqueductal gray, and ventrolateral medulla coordinate the outward expression of emotional states, while peripheral autonomic pathways generate visceral responses and provide interceptive input about the inner state of the body. Rostrally, the limbic sensory cortex in the insula integrates this input into the “feel” of emotions, while the limbic motor cortex of the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC) generate appropriate somatic markers or “visceral feelings” to guide complex behavior and decision-making. The ventral striatum and limbic nuclei of the thalamus provide key outputs from core limbic structures to cortex, essential for weaving the survival functions of emotion into everyday perception and action. Finally, a network of prefrontal regions including the dorsomedial, ventrolateral, ventromedial, and frontopolar cortices are critical for the process of reappraisal: adjusting emotional states based on cognition and context.

All of these structures show varying degrees of sexual dimorphism. Structurally, total brain volume is approximately 10% higher in males, while the gray-white matter ratio is similar in both females and males. Voxel-based morphometry (VBM) studies have shown subtly larger gray matter volume in the amygdala, hippocampus, and parahippocampal cortex in males, as well as increased white matter volume in the anterior temporal lobes, which connect densely to the amygdala. Females have slightly larger gray matter volumes in the ventrolateral and lateral orbitofrontal cortex, which play critical roles in reappraisal of emotional stimuli, as well as in the superior temporal sulcus (STS), which plays a critical role in social cue perception.

**Table I. Descriptive statistics for all variables by gender and age.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young adults</th>
<th>Middle-aged adults</th>
<th>Older adults</th>
<th>Young adults</th>
<th>Middle-aged adults</th>
<th>Older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms</td>
<td>5.50 (0.27)</td>
<td>4.94 (0.26)</td>
<td>4.10 (0.33)</td>
<td>4.29 (0.28)</td>
<td>4.24 (0.27)</td>
<td>3.60 (0.37)</td>
</tr>
<tr>
<td>Rumination</td>
<td>2.04 (0.02)</td>
<td>1.90 (0.02)</td>
<td>1.65 (0.03)</td>
<td>1.98 (0.03)</td>
<td>1.85 (0.02)</td>
<td>1.58 (0.03)</td>
</tr>
<tr>
<td>Suppression</td>
<td>1.95 (0.04)</td>
<td>1.97 (0.04)</td>
<td>2.31 (0.05)</td>
<td>2.03 (0.04)</td>
<td>2.03 (0.04)</td>
<td>2.09 (0.06)</td>
</tr>
<tr>
<td>Reappraisal</td>
<td>2.85 (0.05)</td>
<td>2.81 (0.05)</td>
<td>2.67 (0.07)</td>
<td>2.70 (0.06)</td>
<td>2.57 (0.05)</td>
<td>2.22 (0.07)</td>
</tr>
<tr>
<td>Active coping</td>
<td>2.91 (0.05)</td>
<td>2.93 (0.05)</td>
<td>2.65 (0.07)</td>
<td>3.01 (0.05)</td>
<td>2.84 (0.05)</td>
<td>2.32 (0.07)</td>
</tr>
<tr>
<td>Acceptance</td>
<td>3.02 (0.05)</td>
<td>3.22 (0.05)</td>
<td>3.14 (0.06)</td>
<td>3.04 (0.05)</td>
<td>3.07 (0.05)</td>
<td>2.76 (0.06)</td>
</tr>
<tr>
<td>Social support</td>
<td>3.05 (0.06)</td>
<td>3.03 (0.05)</td>
<td>2.65 (0.07)</td>
<td>2.78 (0.06)</td>
<td>2.66 (0.06)</td>
<td>2.24 (0.08)</td>
</tr>
</tbody>
</table>

Notes: Means for emotion regulation strategies are adjusted for depressive symptom scores; numbers in parentheses are standard deviations for depressive symptoms and standard errors for emotion regulation strategies.
effects in the same regions, and some smaller studies find no significant differences in resting metabolic activity between males and females. Functional magnetic resonance imaging (fMRI) studies have found no sex differences in the functional connectivity of resting-state networks for the “default mode” of introspection and self-reflection, the “executive control” network engaged during cognitive tasks, or the “salience network” activated by potentially relevant events in the sensory environment.

Sex differences in hemispheric asymmetries in emotion pathways

In a majority of studies to date, sex differences in raw structural and functional neuroanatomy are consistently identified, but they are subtle in magnitude. A major exception is a well-replicated sex difference: asymmetry of emotional functions across the two hemispheres of the brain (Figure 2). For example, on resting-state fMRI, the left amygdala shows markedly stronger and more widespread functional connectivity to the rest of the brain in women; conversely, the right amygdala shows stronger connectivity to the rest of the brain in men. During emotional provocation, there is a three-way interaction between sex, hemisphere, and emotional valence. In women, negative stimuli activate the left amygdala, hippocampus, hypothalamus, vmPFC, and ACC, while in men, it is positive emotional stimuli that activate a left-sided network of limbic structures (including amygdala, orbitofrontal cortex, uncus, and temporal pole). Likewise, males show greater activation of the right amygdala in response to sad faces. Subjective sadness is correlated with right amygdala activation in males, but not females.

Sex differences in asymmetry are also apparent in studies of emotional memory. Men watching emotional slides or film clips show strongly lateralized right, but not left amygdala activation which is associated with enhanced memory of the emotionally arousing scenes. Women demonstrate left, but not right amygdala activation associated with better memory for the emotional scenes.

Sex differences in limbic activity are also apparent during more complex emotion-driven prosocial behavior. For example, the anterior insula activates not only during pain, but also empathetically, when witnessing others in pain. In women, this empathetic response is reduced if the other person had previously acted unfairly in a social exchange. However, in men witnessing unfair individuals in pain, the empathetic insular response is abolished entirely. Additionally, in these men, the reward circuitry of the left ventral striatum was also activated asymmetrically. No such “vengeful” response was seen in women, in either hemisphere.

Lesion studies confirm sex differences in functional asymmetry of limbic regions. Among men, right vmPFC lesion caused profound impairments in social and emotional functioning as well as in decision-making, akin to those of the famous case of Phineas Gage. Left-sided lesions produced mild or no impairment. In contrast, among women, it was lesions of the left vmPFC that led to profound social and emotional impairment, while right vmPFC lesions were relatively benign. The same type of sex difference has been observed for the amygdala, with social and emotional deficits arising from right-sided, but not left-sided, lesions in men and left-sided, but not right-sided, lesions in women.

Sex differences in MDD symptom presentation

The case for sex differences in psychiatric illnesses has attracted increasing attention in recent years. Beginning in adolescence, women have a twofold greater risk for MDD compared with men. Although men and women report similar depressive symptoms, women are more likely to recall their symptoms and also experience a greater number of recurring depressive episodes. Classically, atypical (reversed) neuroke vegetative symptoms are more prevalent in women.
pared with men.\textsuperscript{62} Evidence to support higher rates of atypical depression in women is derived from studies of twins and sibling pairs.

An evaluation of more than 200 opposite-sex dizygotic twin pairs who met lifetime criteria for MDD showed that fatigue, hypersomnia, and psychomotor retardation were more prevalent in females, while insomnia and agitation were more likely to occur in males.\textsuperscript{63} The authors suggested that both sex and gender played a role in differential recall as well as hormonal and sociocultural variables.

In an assessment of 94 female twin pairs, Kendler and colleagues identified “severe typical” and “atypical” depression groups. The “severe typical” group was characterized by comorbidity anxiety and panic symptoms, greater functional impairment, and a longer episode duration, while the atypical group reported increased eating, hypersomnia, and more frequent, but shorter episodes. Interestingly, neither neuroticism nor anxiety symptoms were prevalent in the atypical group. However, the absence of male comparison twins limits any conclusions about apparent sex differences in depressive symptoms. This finding was supported by results from a Canadian community epidemiology study which examined the symptom presentation of recurrent depressive episodes in over 650 cases. The authors reported persistent atypical presentation in only 11% of cases, while the majority were either “typical” or did not firmly belong in either category. In both typical and atypical groups, women represented 77% and 75% of the sample, respectively.\textsuperscript{64}

Using a different technique, Moskvina and colleagues compared symptom presentation in more than 400 sibling pairs who met criteria for MDD across European centers. They confirmed a higher frequency of atypical symptoms (fatigue, increased appetite, weight gain, and hypersomnia) in women, who also had higher rates of tearfulness, pathological guilt, morning severity, and loss of reactivity. Female siblings also reported an earlier age of onset and prolonged episode length compared with male siblings. There was also a significant correlation in symptom profiles between female sibling pairs, but not between male sibling pairs or in male-female sibling pairs.

While most studies captured data from white samples, Lai\textsuperscript{65} examined male-female differences in 146 Taiwanese patients: women had greater frequency of sleep disturbance (time to onset and total sleep time), somatic complaints (chest pain, headaches, and appetite loss), as well as sadness and nervousness. Women were also more likely than men to report a reduction in sexual interest, function, and overall satisfaction. In the largest clinical cohort to date of depressed patients participating in a treatment study, 63% were women and they reported greater severity of depressive symptoms, comorbidity of anxiety disorders, binge eating, and somatoform disorders as well as hypersomnia and rejection sensitivity, but less suicidal ideation compared with men.\textsuperscript{67} Men reported a greater number of depressive episodes as well as alcohol and substance use.\textsuperscript{67}

In contrast, Silverstein and colleagues\textsuperscript{68} found that in both the National Comorbidity Survey (NCS14) and the Zurich study,\textsuperscript{69} “pure depression” was comparable in frequency between men and women, while anxious somatic depression was twice as frequent in women. These authors concluded that atypical depressive symptoms did not contribute to male-female differences.

**Sex differences in antidepressant treatment response**

The presence of differing symptom distributions and potential depressive subtypes in men and women suggests that response to antidepressant treatment may also display sex differences.\textsuperscript{70} However, publications in this area provide contrasting results (Table II).\textsuperscript{70-85}

\begin{itemize}
\item **Response to tricyclic antidepressants and monoamine oxidase inhibitors**

Reports from the pre–selective serotonin reuptake inhibitor (SSRI) era suggest that men have higher response rates than women to tricyclic antidepressants (TCAs).\textsuperscript{70-88} A subsequent publication by Quitkin in 2002\textsuperscript{70} used retrospective data to analyze differences in treatment response to TCAs by categorizing participants according to age (<50 years of age and >50 years of age) and sex. A survival analysis indicated that there was no difference in TCA treatment response between older men and older women. However, older women had superior response rates to TCAs when compared with younger women. These results were also replicated in a study by Grigoridiadis and colleagues who found that older women responded more favorably to the TCA desipramine than younger women with response rates of 62% and 34%, respectively.\textsuperscript{84}

Quitkin and colleagues\textsuperscript{70} also evaluated sex differences in response to monoamine oxidase inhibitor (MAOI) therapies. While there was no difference in antidepressant response between older men and older women, there was a difference in response rates between sexes which was accounted for by younger women having a superior response to MAOIs compared with younger men.\textsuperscript{70} These findings contrast with results from a large naturalistic study which concluded that men and women were equally likely to respond to SSRI, TCA, MAOI, and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants.\textsuperscript{77}

\item **Response to SSRIs and SNRIs**

In a study of chronic depression involving 235 men and 400 women, Kornstein and colleagues\textsuperscript{71} identified sex differences in antidepressant response to sertraline and imipramine. There was a statistically significant interaction between sex and treatment, with women having a more favorable response to ser-
traline than imipramine (57% vs 46%), while men were more likely to respond to imipramine than sertraline (62% vs 45%). Moreover, compared with men, women had a greater likelihood of achieving remission over the 12-week treatment period. The inferior response to imipramine compared with sertraline in premenopausal women was attributed to higher attrition among younger women who received the TCA. Using data from the 9-year, multicenter, prospective trial CRESCEND (the Clinical RESearch CENter for Depression), based in South Korea, Yang and colleagues found that women were more likely to respond to SSRIs, supporting previous findings that atypical symptoms are more prevalent in women and respond better to SSRIs. There were no significant differences in response rates between sexes when

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Treatment</th>
<th>Study type</th>
<th>n</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornstein et al, 2000</td>
<td>Sertraline, imipramine</td>
<td>12-Week double-blind trial</td>
<td>635</td>
<td>Women had a superior response to sertraline, men to imipramine</td>
</tr>
<tr>
<td>Martenyi et al, 2001</td>
<td>Fluoxetine, maprotiline</td>
<td>6-Week double-blind trial</td>
<td>105</td>
<td>Women were more responsive to fluoxetine than maprotiline; no difference in men</td>
</tr>
<tr>
<td>Entsuah et al, 2001</td>
<td>Venlafaxine, SSRIs</td>
<td>8 Double-blind, active controlled, randomized trials (4 were placebo controlled)</td>
<td>2045</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Quitkin et al, 2002</td>
<td>TCAs, MAOIs, fluoxetine</td>
<td>8 Placebo-controlled trials and 1 open-label study</td>
<td>1746</td>
<td>Older women had a more favorable response to TCAs than younger women; women had a statistically superior response to MAOIs</td>
</tr>
<tr>
<td>Parker et al, 2003</td>
<td>TCA, SSRI</td>
<td>1 Retrospective study 1 Prospective study</td>
<td>346 162</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Hildebrandt et al, 2003</td>
<td>TCA, SSRI, MAOI</td>
<td>3 Double-blind, randomized controlled trials</td>
<td>292</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Grigoriadis et al, 2003</td>
<td>SSRI, nefazodone, or venlafaxine</td>
<td>8-Week double-blind study</td>
<td>201</td>
<td>Younger compared with older women were more responsive to serotonergic antidepressants</td>
</tr>
<tr>
<td>Scheibe et al, 2003</td>
<td>TCAs, SSRIs, SNRIs, MAOIs, RIMAs</td>
<td>Retrospective study</td>
<td>385</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Wohlfarth et al, 2004</td>
<td>TCAs</td>
<td>30 Randomized, placebo controlled trials</td>
<td>3886</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Cassano et al, 2004</td>
<td>Fluoxetine</td>
<td>8-Week open-label study</td>
<td>320</td>
<td>No sex differences</td>
</tr>
<tr>
<td>Khan et al, 2005</td>
<td>SSRIs, SNRIs</td>
<td>15 Randomized placebo-controlled trials</td>
<td>323</td>
<td>Women responded better to SSRIs and SNRIs than men</td>
</tr>
<tr>
<td>Kornstein et al, 2006</td>
<td>Duloxetine</td>
<td>7 Randomized, double-blind, placebo controlled trials</td>
<td>896</td>
<td>No sex differences in antidepressant response, but women on duloxetine compared with placebo had a significant reduction in pain severity</td>
</tr>
<tr>
<td>Grigoriadis et al, 2007</td>
<td>TCAs, SSRIs, SNRIs</td>
<td>8-Week, open-label, flexible-dose trial</td>
<td>205</td>
<td>Men responded more favorably to SSRIs and venlafaxine than women</td>
</tr>
<tr>
<td>Young et al, 2009</td>
<td>Citalopram</td>
<td>12- to 14-Week, open-label, flexible dose study</td>
<td>2876</td>
<td>Women were significantly more likely to achieve remission than men during citalopram treatment</td>
</tr>
<tr>
<td>Grigoriadis et al, 2010</td>
<td>Desipramine</td>
<td>8-Week, double-blind, flexible-dose study; women only</td>
<td>113</td>
<td>No sex differences; older women showed better response to desipramine than younger women (trend)</td>
</tr>
<tr>
<td>Yang et al, 2011</td>
<td>SSRIs, newer dual antidepressants, other antidepressants</td>
<td>12-Week naturalistic cohort study</td>
<td>723</td>
<td>Women were significantly more likely to respond to SSRIs than men</td>
</tr>
</tbody>
</table>

**Table II.** Sex- and age-related differences in antidepressant treatment response.

**Abbreviations:** MAOI, monoamine oxidase inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

data from seven randomized double-blind, placebo-controlled trials of duloxetine were pooled. On the other hand, compared with men, duloxetine-treated women showed a greater reduction in overall pain severity scores.81

- **Other medications**
  
  Data are limited on sex differences in response rates to newer antidepressants and augmentation therapies for depression. Recent evidence suggests that agomelatine, which is a novel melatonergic antidepressant with good tolerability has equal efficacy in men and women.30

- **Limitations**
  
  Gonadal hormones, specifically estrogen, which is a substrate for cytochrome P450 (CYP) 3A4 and CYP1A2 as well as an inhibitor of CYP1A2, may impact antidepressant metabolism by enhancing response to SSRIs or inhibiting response to TCAs.82 However, failure to demonstrate differences may also relate to methodological limitations in published studies. Not all studies stratified their samples according to the hormonal status of women (pre/perimenopausal vs postmenopausal); several studies were underpowered due to small sample size.70

- **Neurostimulation therapies**
  
  Sex differences may also be relevant in response to anatomically targeted device therapies such as repetitive transcranial magnetic stimulation (rTMS)82 and deep brain stimulation (DBS). Given the differential roles of left- and right-hemisphere limbic structures in negative emotions in men and women, tailoring the parameters of rTMS according to the sex of the patient could potentially improve antidepressant efficacy. In DBS for MDD, electrodes are typically implanted bilaterally in the subgenual cingulum, an area of the vmPFC that is densely connected with the amygdala. Stimulation is typically bilateral. Although DBS is effective in many refractory depression cases, approximately one-third still do not respond to treatment.83 Again, based on the lesion and neuroimaging evidence above, adjusting stimulation laterality for sex could improve the response rates.

**Conclusion**

We have reviewed key studies looking at sex differences in emotional behavior, brain circuits, and response to treatment. It seems that gender—or the social expectations of both patient and therapist—plays a role in establishing differences where differences have been established. In terms of brain circuits, sex differences are particularly prominent in limbic structures relevant to the generation and expression of emotional states, such as the amygdala, insula, and medial prefrontal cortex. The most striking differences appear as an interaction between sex, hemisphere, and emotional valence. For negative emotions, men preferentially recruit right hemisphere structures, while women depend more on left hemisphere structures. However, these data are still controversial and without clear replication. This suggests that individual differences may be extremely important, especially for the success of some of the newest brain-targeting therapies. These individual differences may also be at play in the noted therapeutic efficacies of different treatment classes of antidepressants. Importantly, however, with the exception of the behavioral work which has a long history, serious exploration into sex differences in brain and treatment response are emerging fields. As such, they will need to develop awareness in experimental design regarding the age of participants, sex, and reproductive life stage as well as, within that stage, reproductive status and hormonal levels. Gender expectations may also need to figure into any cellular and genetic research as the emerging field of epigenetics suggests that social location will also affect biology. The challenge for the future is to determine when a sex/gender difference makes a difference.

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**References**


Keywords: antidepressants; emotion; gender differences; major depressive disorder (MDD); neurobiology; neuroimaging; sex differences; symptom presentation; treatment response

DIFFÉRENCES ÉMOTIONNELLES SELON LE SEXE ET LE GÉNRE

Les différences sexuelles biologiques commencent en utero et se développent tout au long de la vie en fonction des processus biologiques et de l’expérience. Le concept de genre nécessite de séparer les constructions biologiques (sexes) et sociales (genre) et de s’intéresser au rôle joué par les hormones et les gènes dans la mise en place des différences émotionnelles, et plus particulièrement de celles qui sont dues à la différenciation sexuelle du fœtus et au cycle reproductif. Des techniques de neuro-imagier fonctionnelles de plus en plus sophistiquées mettent en évidence les différences sexuelles cérébrales et leur influence sur les différentes expressions des émotions. Il existe peu de preuves montrant des différences de symptômes entre les hommes et les femmes dans la dépression et les données sur les différences de réponse aux antidépresseurs selon le sexe dans la dépression majeure sont contradictoires.
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No one particular region has abnormal activity in depression; rather, there is an imbalance in activity between regions. Hence, the whole network is altered, apparently undergoing changes that imbalance and shift the neural activity distribution across different regions. How that works in detail, though, remains unclear. This suggests that in depression, rather than alteration of one particular emotion, all emotions are altered in an abnormal way.

Emotions are fundamental to our life and are largely altered in many psychiatric disorders, such as depression. Recent imaging studies investigated various types of emotions, such as anger, fear, sadness, disgust, and happiness, aiming to “localize” them in specific regions of the brain. These studies reveal that many regions—including the amygdala, insula, ventro- and dorsolateral prefrontal cortex, ventro- and dorsomedial prefrontal cortex, periaqueductal gray, and anterior cingulate cortex—are implicated in various types of emotions, suggesting that emotions are mediated by different neural networks rather than specific regions. Complicating matters further, the brain’s spontaneous or intrinsic activity, eg, resting-state activity, is also closely related to emotion processing. Recent studies demonstrate that the level of resting-state activity may be modulated by preceding emotions, suggesting that these emotions are somehow encoded in a yet unclear way into the neural patterns of the brain’s intrinsic activity. Thus, the neural activity we observe when experiencing emotions may be the result of the integration of extrinsic stimuli and intrinsic activity. This is highly relevant in depression, where the brain’s intrinsic activity is abnormally imbalanced, with resting-state hyperactivity in medial regions and resting-state hypoactivity in lateral regions.

Emotions and the regions of the brain

A number of imaging studies using functional magnetic resonance imaging have been conducted over the last 10 years both in healthy and depressed subjects. Focusing on the main findings in the main regions of the brain in healthy subjects and the implications for depression, this general overview of the numerous imaging studies on emotion will first take a brief look at the methodology involved.

Emotion paradigms

Imaging studies on emotion apply different kinds of paradigms. The bulk of the studies use visual stimulation. Subjects view emotional pictures—eg, faces that are sad, happy, angry, etc—or they watch videos of emotional scenes. Other studies apply auditory stimulation as well, using emotional tones, for example. In the study design, it is also important to consider the task associated with the respective emotional stimulus. Subjects may be asked to merely perceive the emotional stimuli without much self-involvement. Alternatively, they may be required to imagine themselves in that particular scene and to experience the respective emotion.
Besides mere perception and actual experience of emotional stimuli, other studies require a judgment to be made, where subjects have to judge the emotional stimulus as positive or negative, for example, either during or immediately following its presentation. Finally, subjects may be asked to recall and retrieve specific emotional experiences from their own life. This introduces a strong memory component into the design. These so-called task-related effects are important to consider since they may confound and mix with the neural effects related to the emotional stimulus effect, the stimulus-related effects. For instance, it has been shown that task-related effects like judgment are associated with the lateral prefrontal cortex, while mere perception and actual experience of the same emotional stimulus yield neural activity in the medial prefrontal cortex. Hence, we have to distinguish between task-related and stimulus-related effects.

Brain regions involved in processing emotion

Various regions of the brain are implicated in emotion processing (see meta-analyses1-3). One core region is the amygdala, a subcortical region that lies anterior to the hippocampus. The amygdala has been shown to be involved in emotion processing in both animal and human studies, and has therefore often been considered “the emotion region” of the brain. More specifically, emotions yielding activity changes in the amygdala include fear, disgust, and anger, i.e., negative emotions. Another subcortical region especially implicated in the processing of fear is the periaqueductal gray (PAG). The PAG is a convergence, or node station, for the confluence of interoceptive stimuli from the body, exteroceptive sensory stimuli from the sensory modalities, and motor stimuli for generating movement and action. This makes it perfectly suitable to be involved in emotion. Fear and anger have been especially associated with neural activity in the PAG.

The hippocampus, lying posterior to the amygdala, has also been implicated in emotion processing. The entorhinal cortex, especially, as part of the hippocampal complex has been shown to be recruited during disgust, sadness, anger, and fear. This is important as the hippocampus is a central focus in depression, in the context of stress and cortisol-related changes as an important part of the pathophysiology. How the stress-related hippocampal changes in depression are related to the abnormal emotion processing in this and other regions, however, remains unclear.

Another region centrally implicated in emotion processing is the insula. The insula lies on the outer surface of the brain and, like the amygdala, receives both interoceptive, e.g., vegetative, input from the body and exteroceptive input from the various sensory modalities. Such convergence seems to make the insula an ideal candidate for emotion processing since emotions are supposed to result from the integration between interoceptive and exteroceptive stimuli. One emotion prominently shown to consistently activate the insula is disgust. Several studies on disgust have been conducted and demonstrated strong insula involvement. This has often led to the assumption that the insula may be specific to the processing of disgust. However, the insula has been shown to be implicated in other emotions as well, such as anger and fear, in the same way that disgust also recruits other regions like the occipital cortex, the amygdala, and the lateral prefrontal cortex.

Another region involved in emotion processing is the orbitofrontal cortex, to which the insula sends many projections. As are the insula and the amygdala, the orbitofrontal cortex too has been associated with different emotions. Most prominent among them is anger, but fear and disgust also seem to recruit this region. The orbitofrontal cortex is closely related to the medial prefrontal cortex, which includes the ventro- and dorsomedial prefrontal cortex (vmPFC and dmPFC, respectively). The vmPFC and dmPFC have both been associated with sadness, fear, and happiness. The dmPFC may be particularly involved in reflection upon the emotional experience, as for instance during evaluation or judgment, while the vmPFC may be more involved in the experience or perception of the emotion itself.

Turning laterally, we encounter the dorso- and ventrolateral prefrontal cortex (dIPFC and vPFC, respectively). Both regions have been associated with emotion processing in general. Negative emotions may be more associated with the left vPFC and dIPFC, while positive emotions are supposed to involve the right side. Moreover, the dIPFC, especially, has been associated with more cognitive aspects of emotion processing, such as cognitive control, executive attention, and evaluation/judgment of emotions. The vPFC is especially recruited when showing emotional faces, possibly related to the involvement of this region in face processing, particularly where one’s own face is concerned.

Closely related is the cingulate cortex. The cingulate cortex comprises the sub/pregenual and supragenual anterior cingulate cortex (PACC and SACC, respectively) and the posterior cingulate cortex (PCC). The PACC has been associated with sadness in particular, but also with other emotions like anger and disgust. The PACC receives direct interoceptive

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<th>Selected abbreviations and acronyms</th>
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<tr>
<td>dIPFC</td>
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<td>DMN</td>
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<td>dmPFC</td>
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<td>PACC</td>
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and exteroceptive input from the insula and amygdala, while the SACC interacts with the lateral prefrontal cortex. Correspondingly, the SACC is often associated with the cognitive control of and executive attention to emotions in general. Finally, the PCC, lying posterior, is closely connected to the hippocampal complex and is therefore involved in memory processing, especially the retrieval of episodic or autobiographical memories. The PCC has also been implicated in a range of emotions, including anger, fear, and sadness.

Other regions implicated in emotion processing include the visual, or occipital, cortex and the temporal cortex. While predominantly accounting for visual processing, the occipital cortex has often been demonstrated to show heightened activity during different emotions, especially negative ones such as fear, anxiety, sadness, and disgust. This cannot be due to the type of stimuli since the purely visual processing aspects are usually cancelled out by comparing visual emotional stimuli with visual nonemotional stimuli. Hence, it seems that an emotional component enhances neural activity in the occipital cortex during visual processing. The occipital cortex is strongly implicated, especially in studies that require subjects to imagine specific emotions, possibly related to the fact that imagery is often visual. Moreover, emotional pictures often elicit strong activity changes in the occipital cortex, as distinguished from films or faces, for instance.

Emotions are mediated by neural networks rather than specific regions of the brain

What do these findings tell us about the relationship between emotion and the brain? Confusing as these findings are, they indicate that one particular emotion is not associated with one or two particular regions in the brain. For instance, almost all studies demonstrate that specific emotions, such as disgust, fear, and anger, do not recruit one particular region, but many as indicated above. As each emotion recruits multiple regions, emotions seem to be mediated by neural networks rather than specific regions. One may thus want to speak of a network—rather than a region-based—approach to emotion.

Brain regions are associated with specific processes rather than specific emotions

Moreover, there is no region that is involved only in one particular emotion. Instead, each region seems to be implicated in several emotions. The same region may make different contributions to the different emotions whose processing it mediates. What exactly these contributions are, though, we currently do not know. Thus, it cannot be said that one region’s neural activity and processing is specified for a particular emotion, or more generally put, a specific emotional content. Instead, the regions seem to mediate specific processes, with these processes being implicated in different emotions and their respective contents. One may thus want to speak of a process-based rather than content-based approach to the regions.

What is the relevance to depression?

One may now raise the question as to why and how all that is relevant to depression. The various forms of depression, such as major depressive disorder or bipolar depression, show changes in almost all of these regions. For instance, studies in major depressive disorder demonstrated abnormal activity during emotional stimulation in the PACC, SACC, insula, dIPFC, and vPFC. These regions are also implicated in bipolar depression, though possibly in different ways. What the findings suggest is that no one particular region has abnormal activity in depression; rather, there is an imbalance in activity between regions. Hence, the whole network is altered, apparently undergoing changes that imbalance and shift the neural activity distribution across different regions. How that works in detail, though, remains unclear.

This suggests that in depression, rather than alteration of one particular emotion, all emotions are altered in an abnormal way. The neural network seems to be imbalanced, which in turn may lead to abnormal processing of the various emotional contents. As mentioned above, however, we do not understand the exact neural processes mediated by the various regions and neural networks, making it difficult to determine the exact pathophysiological mechanisms in depression.

Emotions and the brain’s intrinsic activity

This overview has thus far focused mainly on neural activity related to particular stimuli, eg, emotional stimuli. This is described as stimulus-induced activity that describes how stimuli extrinsic to the brain, eg, from the environment (or the body), yield neural activity changes in the brain. Such extrinsic stimulus-induced activity originating from stimuli outside the brain must be distinguished from neural activity originating from the brain itself and thus intrinsic to it. Such intrinsic activity is often described as spontaneous activity or in an operationalized form as resting-state activity signaling the absence of specific extrinsic stimuli.

Historical “extrinsic view” and “intrinsic view” of the brain

While the notion of intrinsic activity in the brain has been around for almost 100 years, it has recently come to the foreground again, especially in brain imaging. What is the brain and how does it operate? This was already the subject of controversial discussion in the early days of neuroscience at the beginning of the 20th century. One view of the brain, favored by the British neurologist Sir Charles Sherrington (1857-1952), assumed the brain and the spinal cord to be primarily reflexive. Reflexive means that the brain reacts in predefined and automatic ways to stimuli. Thus, the stimuli from outside the brain, originating extrinsically in either the body or environment, are assumed to determine completely and exclusively the subsequent neural activity. The resulting stimulus-induced activity, more generally any neural activity in the brain, is consecutively traced back to the extrinsic stimuli. This may be considered an “extrinsic view” of the brain (Figure 1A, page 284). For every
view there is an opposing view, however. An alternative view was already suggested by one of Sherrington’s students, Thomas Graham Brown. In contrast to his teacher, he suggested that the brain’s activity, i.e., in the spinal cord and brain stem, is not primarily driven by extrinsic stimuli from outside the brain, i.e., the body and environment. Instead, the spinal cord and brain stem show spontaneous activity originating intrinsically within themselves. Other subsequent neuroscientists such as Karl Lashley, Kurt Goldstein, and Wolfgang Köhler followed Brown’s line of thought and assumed the brain to show intrinsic activity. This may be considered an “intrinsic view” of the brain.

◆ **Stimulus-induced activity: interaction between intrinsic activity and extrinsic stimulus**

The assumption of intrinsic activity generated inside the brain itself has major implications for how we conceive stimulus-induced activity. What we as observers describe as stimulus-induced activity and usually associate with the stimulus itself must then be regarded as the hybrid result of a specific interaction between the brain’s intrinsic activity and the extrinsic stimulus.

Stimulus-induced activity and any neural activity in the brain must consecutively be traced back to a double input that originates in both the brain’s intrinsic activity and the body’s and the environment’s extrinsic stimuli (*Figure 1B*).

◆ **Present status: extrinsic vs intrinsic view**

Following this rather abbreviated history of neuroscience, let’s look at the present. The dichotomy between intrinsic and extrinsic views of the brain is still just as controversial and has most recently resurfaced, especially in functional brain imaging (see examples 4, 5). Let’s start with the extrinsic view.

Many domains of neuroscience, ranging from cellular over regional to behavioral, rely on experimental application of specific stimuli and tasks to probe neural activity. By comparing different stimuli and tasks, the resulting differences in neural activity are associated with the respective stimuli or tasks. Consequently, the experimental requirements may prime and draw us toward the extrinsic view. The extrinsic view has been predominant in behaviorism which, according to authors like Jaak Panksepp, finds its continuation in the cognitive neuroscience of our days.

However, the extrinsic view of the brain has recently been challenged again on several grounds. Even in the resting state, i.e., in the absence of any (specific) extrinsic stimuli, the brain...
shows a rather high degree of metabolism, consuming, for instance, about 20% of the body’s overall energy budget (and oxygen fraction).\textsuperscript{4,5,7–9}

Using functional imaging, this high metabolism has been especially observed in a particular set of regions—the default-mode network (DMN)—which includes various anterior and posterior cortical midline structures as well as the bilateral posterior parietal cortex.\textsuperscript{4,5,9–11} The high degree of metabolism is indicative of continuously ongoing high levels of neural activity even in the absence of (specific) extrinsic stimuli, i.e., in the resting state of the DMN. However, other regions outside the DMN also show spontaneous neural activity, independent of any extrinsic stimuli. This has been demonstrated in the auditory and visual cortex, thalamus, hippocampus, olfactory cortex, cortical midline regions, prefrontal cortex, motor cortex, and other subcortical regions, such as the brain stem and midbrain.\textsuperscript{6,9} The metabolic and neuronal signs of intrinsic activity are further complemented by behavioral evidence; spontaneous behavior, such as seeking or behavioral activation, can be observed even in the absence of extrinsic stimuli.\textsuperscript{6} Which view holds—the intrinsic or the extrinsic one? Rather than choosing one view and dismissing the other, the brain itself may force us to reconcile both views. Any neural activity in the brain may be assumed to result from the interaction between the brain’s intrinsic activity and the extrinsic stimuli from the body and environment. In place of intrinsic and extrinsic views, we may need to investigate how intrinsic activity and extrinsic stimuli interact with each other in order to understand the brain’s neural activity.

\textbf{Relevance to processing of emotions}

Why is all that relevant for the neural processing of emotions? It’s relevant because emotions may result from the interplay between intrinsic activity and extrinsic stimuli. Most recently, single studies demonstrated that there is direct interaction between extrinsically induced emotion and the brain’s intrinsic activity.

Focusing on emotions, a recent study\textsuperscript{12} investigated the impact of fearful, joyful, and neutral movie clips (50-s presentation) on subsequent resting-state activity (90-s period with eyes closed). After the resting-state period, participants were asked about their thoughts, revealing that personal relevant issues in the subjects’ thoughts were increased after neutral movies, increased, but less so, after joyful movies, and significantly decreased after fearful movies. These results show a clear behavioral effect or better psychological effect of emotions on thought content in subsequent resting-state periods; fearful movies seem to leave the strongest traces on thought content of subsequent resting states.

Resting-state neuronal activity in subcortical regions (pallidum, anterior thalamus, and hypothalamus) was higher after viewing fearful movies than after viewing neutral movies (resting-state activity greater after fearful stimulation than after neutral stimulation). Most interestingly, the reverse comparison (resting-state activity greater after neutral stimulation than after fearful stimulation) revealed more pronounced signal changes in various regions of the DMN (vmPFC, PACC, dmPFC, superior temporal gyrus) (see analogous overlap between emotion processing and the DMN\textsuperscript{13,14}).

This means that the inclusion of fearful emotions in the preceding movie had a clear effect on the level of subsequent resting-state activity. The stronger resting-state effects of the preceding emotional movies are further confirmed by the more delayed recovery from the signal changes during the resting-state period (90 s) after emotional movies.

Taken together, it seems that emotions are closely related to the resting-state activity. Studies show that emotions affect the level of activity in the resting state, thus indicating what can be described as stimulus-rest interaction.\textsuperscript{15} Conversely, one may also expect the resting-state activity to have an impact on emotions during presentation of particular stimuli. While such rest-stimulus interaction has been described in perception and cognitive functions, it remains to be demonstrated for emotion. The degree and intensity of emotions in psychological regard and the recruitment of particular regions and networks may then depend not only on the extrinsic stimulus itself and its associated emotional content, but also on the characteristics of the brain’s intrinsic activity.

\textbf{Relevance of resting-state activity to depression}

Why is all that relevant to depression? To start with, human and animal studies in depression demonstrate abnormal resting-state activity in various regions. For instance, the resting-state activity in the PACC seems to be abnormally high in major depressive disorder, while that in the dlPFC is abnormally low in these patients (see overview\textsuperscript{16}). Given the above-described findings, it seems certain that such resting-state abnormalities must have an impact on subsequent emotion processing in the various regions described above.

One may consequently hypothesize that some of the psychological and neural abnormalities observed in emotion processing in depression may be related to yet-to-be-specified abnormalities in intrinsic activity. In addition to providing insight into the pathophysiology of depression, this may lead to opportunities for more specific and effective therapeutic intervention. For instance, if we understand the biochemical mechanisms underlying the resting-state abnormalities in depression, we may be able to design drugs that specifically target those mechanisms and may thereby normalize subsequent emotion processing. That, however, is a scenario of the future, hopefully the near future.

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ÉMOTIONS ET NEURO-IMAGERIE

Les émotions, essentielles dans notre vie, sont très altérées dans de nombreux troubles psychiatriques comme la dépression. Des études récentes d’imagerie ont cherché à localiser dans des régions spécifiques du cerveau différents types d’émotions comme la colère, la peur, la tristesse, le dégoût et la joie. Ces études ont montré que de nombreuses régions (amygdale, insula, cortex préfrontal ventro- et dorsolatéral, cortex préfrontal ventro- et dorsomédian, substance grise périaqueducale, cortex cingulaire antérieur) sont concernées par différents types d’émotions, ce qui semble indiquer le traitement des émotions est plus axé de réseaux neuronaux que de régions spécifiques du cerveau. Ce schéma se complique encore du fait que l’activité spontanée du cerveau ou activité intrinsèque (c’est-à-dire l’activité à l’état de repos) est également étroitement impliquée dans les processus émotionnels. Des études récentes montrent que le niveau d’activité de repos peut être modulé par des émotions antérieures, comme si ces émotions étaient, d’une certaine façon et par des voies encore mal connues, encodées dans les modèles neuronaux de l’activité cérébrale intrinsèque. L’activité neuronale que nous observons lors d’émotions ressenties pourrait donc résulter de l’intégration de stimuli extrinsèques et d’une activité intrinsèque. Ceci prend tout son sens dans la dépression où l’activité intrinsèque cérébrale est anormalement déséquilibrée avec une hyperactivité de repos dans les régions médiales et une hypoactivité de repos dans les régions latérales.
Depressed mood and anhedonia are the two core symptoms of major depression as defined in the Diagnostic and Statistical Manual of Mental Disorders, but both symptoms are more complex than generally thought. The differentiation between depressed mood and sadness or between depressed mood and bereavement remains a clinically relevant question in daily practice. While the former is rather a mood or affect state and is usually considered independent from loss, the latter is an emotion and is usually considered as being linked to a loss situation. However, clinical reality shows that, especially in first episode depression (less in recurrent depression), patients frequently report stressful life events often linked to loss. Anhedonia, or lack of interest or pleasure, is a compound criterion, since loss of interest (appetitive or motivational anhedonia) and loss of pleasure (consummatory anhedonia) are different phenomena. Another clinically relevant question is whether the opposite of anhedonia is absence of anhedonia or whether it is the presence of positive mood and well-being. The tools most frequently used to assess change during antidepressant treatment give significantly more attention to depressed mood than to anhedonia. This is worrying, since it is in sharp contrast with what patients expect from treatment. Indeed, it has been documented that patients consider the restoration of positive mental health (optimism, vigor, self-confidence) to be the most important expectation. In conclusion, more careful differentiation between (normal) sadness and depressed mood could probably enhance diagnostic accuracy in depression, and a more careful taking into account of positive mood would probably be beneficial to the depressed patient.

Distinguishing between sadness and depression is important, but not always easy. Both are often associated with loss..., but the difference is that the depressed individual feels, and often actually is, incapable of dealing with the loss: the depression must be resolved before the individual can attempt to deal with the loss. By contrast, in simple sadness, the individual is capable of taking another look at the source of trouble and doing something about it."

From sadness to depressed mood and from anhedonia to positive mood and well-being

by K. Demyttenaere, Belgium

In the more recent versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the two core symptoms of depression are depressed mood and lack of interest or pleasure. This is in contrast with the more recent versions of the International Classifications of Diseases (ICD), where three core symptoms of depression are mentioned: depressed mood, lack of interest or pleasure, and fatigue. The present paper focuses on depressed mood and how it is related to sadness, and on anhedonia and how it is related to positive mood or well-being.

In daily life, we all experience positive and negative emotions, positive and negative affect, positive and negative mood, and it is probably a lifelong challenge to find a balance between them.
German E. Berrios, making an attempt to carefully order the words mood, affect, sentiment, emotion, and passion, and to help us out of the terminology confusion, cites Ribot1:

Sentiment, emotion and passion have been customarily distinguished from mood, affect and feeling in terms of criteria such as duration, polarity, intensity, insight, saliency, association with an inner or outer object, bodily sensations and motivational force. Sentiment, emotion and passion are defined as feeling states that are short-lived, intense, salient, and related to a recognizable object. Mood and affect, on the other hand, are defined as longer lasting and objectless states capable of providing a sort of background feeling tone to the individual.

From sadness to depressed mood
Izard stated that sadness is generally considered to be a negative emotion, an emotional response to separation, death, disappointment, failure to achieve an important goal, or to the sorrow of another. He but he also stated that we too often forget that sadness can be an appropriate response: for example, to the death of someone you love. Shared sadness can reunite a family or friends, can strengthen the sources of social support, can invite you to slow down the pace of your life, can communicate to the self that all is not well, can motivate one to renew and strengthen bonds with others, and can play a role in empathy. Distinguishing between sadness and depression is important, but not always easy. Both are often associated with loss (death, loss of a companion, the loss of friends or a love relationship, or even less easily definable losses), but the difference is that the depressed individual feels, and often actually is, incapable of dealing with the loss: the depression must be resolved before the individual can attempt to deal with the loss. By contrast, in simple sadness, the individual is capable of taking another look at the source of trouble and doing something about it. It is, however, well documented that stressors (most often loss situations) are more frequently found in the months preceding a first episode depression than in the months preceding recurrent episode depression, where new episodes seem to become more and more independent of life stressors or losses. So from a qualitative point of view, first episode depression seems to be closer to sadness as an emotion, while recurrent depression seems to be closer to depressed mood or depressed affect. The wording of the DSM diagnostic criteria for depression seems to combine both aspects: depressed mood is defined as feeling sad or empty as indicated by self-report or as appearing tearful as observed by others.4

If we accept that sadness is a negative emotion related to separation or loss and that depressed mood or depressed affect is a longer lasting and maybe more objectless state, the subsequent versions of psychiatric classification systems seem to have struggled with this difference. Indeed, neither the Feighner criteria nor the Research Diagnostic Criteria (RDC) contained an exclusion for bereavement or any other normal reactions, although they did require researchers to ascertain during their interview with patients whether bereavement was present.10,11 But DSM-III did contain bereavement as an exclusion criterion, where it was the single exception to defining sad or depressed mood as a depressive symptom. However, DSM-III overlooked the fact that reactions to other types of loss may have similar features to bereavement; for example, reactions to separation, illness, or economic reversal. Reactions to these types of loss were hence not included, perhaps because they could lack the relatively clear-cut nature of bereavement. An intermediate solution has been proposed to differentiate between bereavement and depression on top of bereavement: is the sadness a proportionate response to the real loss? This does not seem to solve the problem, however, since the discussion then just shifts to what is proportionate or not. Moreover, it has also been argued that the bereavement issue then becomes an etiological one that has no place in a theory-neutral manual, which DSM claims to aim to be. Aside from “disproportionate,” other attempts at exclusions—from the exclusion have been “when no close temporal relationship (eg, 3 months?) between bereavement and depression was found” and “when the bereavement reaction was too long lasting (2 months? 6 months?),” but again, these specifications are debatable and not very helpful. The additional diagnostic criteria for “adjustment disorder with depressed mood” are also not very helpful in qualitatively differentiating the two mood states.

Ghaemi takes this discussion back to Freud, who compared bereavement and depression (Mourning and Melancholia, 1917) and found that depression is phenomenologically similar to mourning and that what happens in mourning could provide the key to depression: sad at our loved one’s death, guilty about the anger toward him, we turn our anger inward, repressing its outward expression, and become even sadder. Freud hypothesized that pathological depression also involved these kinds of feelings toward others, repressed by an anger turned inward and directed at oneself. It becomes clear that sadness here can be understood as being part of a broader domain that also includes some degree of emotional emptiness, shame, humiliation, or loss of self-esteem. In a mourning process, the world seems to be empty, while in depression, the world and the self seem to be empty.

Ghaemi then brings this discussion to two opposite models of depression, leaving the “bereavement-depression” debate and focusing more on cognitive distortions as being at the origin of depressed mood. It is therefore no longer the de-
pressed or sad mood that specifies depression, but the cognitive distortions around it. The “learned helplessness” model indeed postulates that individuals develop depression in adulthood based on experiences earlier in life in which they suffered, but from which they had no means of escaping. They retain these feelings even when escape routes are later offered: they learned to be helpless, and they remain so. Hence, depressed patients would suffer from depression because of these cognitive distortions, present in response to sadness in depressed patients, but absent in “normal” sadness. By contrast, the “depressive realism” model, based on experiments with college students that involved guessing when they did and did not have control over an outcome through their actions in a test situation, postulates that it is not the depressed individuals, but rather the healthy nondepressed individuals that have cognitive distortions, not seeing the world too much as it is, with all its pain and mortality and with all our weakness and cosmic insignificance as individuals. Depressed patients, hence, would suffer from depression because of their lack of cognitive distortions. Depression might seem simple, but it is definitely not.

From anhedonia to positive mood and well-being

The second core symptom in the DSM criteria for depression is lack of interest or pleasure. A more careful look at the way this symptom has been treated in different classifications reveals the ambivalence or the hesitations regarding the importance to be given to this symptom.

The Feighner criteria had only one necessary condition for the diagnosis of depression (dysphoric mood marked by symptoms such as being depressed, sad, despondent, or hopeless), and “loss of interest in usual activities” was only one of the minimum five additional symptoms needed to make the diagnosis of depression (at the same level as loss of appetite, sleep difficulty, loss of energy, agitation, guilt feelings, slow thinking, and recurrent suicidal thoughts). From DSM-III onward, anhedonia (loss of interest and pleasure) became a core symptom of depression, at the same level as depressed mood.

Anhedonia (lack of..., loss of...) is considered to be opposite to the notions of “positive mental health,” (“positive emotions,” “positive affect,” “positive mood”), and these notions continue to elicit conflicting opinions. Health can be seen as merely the absence of illness: illness is defined positively and health negatively. The World Health Organization (WHO) defined “health” as a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity (WHO, 1948). As Ghaemi stated, other authors are opposed to this view and reject the “unattainable wholeness of body, mind, and soul,” while arguing that it is the presence of disease that can be recognized, not the presence of health. In any case, the question remains as to whether the opposite of anhedonia is the absence of anhedonia or the presence of hedonia; in other words, is lack of anhedonia enough to consider somebody to be in “positive mental health” or should there be positive hedonia?

Another problem with symptoms of anhedonia is that they are considered as a compound diagnostic criterion: loss of interest (appetitive or motivational anhedonia, “wanting”) and loss of pleasure (consummatory anhedonia, “liking”) in response to stimuli that were previously perceived as rewarding. This aggregation hence lacks precision, and from a psychological as well as neurobiological point of view, these two subsymptoms are not the same.

One could even go one step further and try to “read” other depressive symptoms as being decreased hedonic function: depressed mood as decreased positive affect, fatigue as diminished motivation and/or decreased energy to pursue enjoyable and goal-directed activities, and social withdrawal as reduced enthusiasm for interactions with others or difficulty obtaining enjoyment from these interactions. One could also differentiate between experiencing positive emotions (pride, enthusiasm, determination, strength, inspiration, joy, enjoyment, surprise, pleasure, excitement, vigor, etc) and the anticipation of responding with positive emotions to pleasurable situations (I would enjoy seeing other people’s smiling faces, I would enjoy a warm bath or refreshing shower, I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread, someone complimenting me would have a great effect on me, someone I am very attracted to asking me out for coffee would have a great effect on me, etc). The dysregulation of positive affect in depression could even be further differentiated between an elevated threshold for activating positive affect, a less intense response once positive affect is activated, difficulty sustaining a positive affect response, failure to activate positive affect in appropriate contexts, or insufficient devotion of cognitive resources to initiating, sustaining, or enhancing a typical internal positive affect response.

Assessment of treatment effects on sadness and depressed mood, on anhedonia, positive mood, and well-being

The assessment of change during antidepressant treatment is usually carried out with an observer rating scale: the Hamilton Depression Rating Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). The two core
symptoms of the DSM diagnostic criteria are included in the rating scales to a different degree, but in any case lose their "privileged" position. Sad or depressed mood is well represented in both scales, but anhedonia has a more marginal position in both scales.

The 17-item HAM-D also gives more attention to negative affect items than to anhedonia: depressed mood (sadness, hopelessness, helplessness, worthlessness; hence, not only referring to affect, but also to cognitions), psychological anxiety (subjective tension and irritability, worrying), and somatic anxiety. Again, only one item is more or less referring to anhedonia: work and activities (thoughts and feelings of incapacity; fatigue or weakness; loss of interest in activities, hobbies, or work; decrease in actual time spent in activities or decrease in productivity; stopping working—hence, not only referring to anhedonia, but also to functioning).22

The 10-item MADRS has three negative affect items: apparent sadness (representing despondency, gloom, and despair [more than just ordinary transient low spirits]), reported sadness (representing depressed mood, low spirits, despondency, or feelings of being beyond help without hope), and inner tension (representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread, or anguish). Only one item refers to anhedonia, although in the higher scores, there is a reference to the complete inability to feel positive as well as negative emotion: inability to feel (representing the subjective experience of reduced interest in the surroundings or in activities that normally give pleasure, up to the experience of being emotionally paralyzed, unable to feel anger, grief, or pleasure).23

The rather marginal place of anhedonia is hence somewhat in contrast with the DSM criteria. What is more worrying, however, is that this is in sharp contrast with what patients themselves expect as an outcome from treatment when suffering from depression. Zimmerman showed that from a patient perspective, the rank order of the most important expectations from antidepressant treatment are first, presence of positive mental health (optimism, vigor, self-confidence); second, feeling like your usual, normal self; third, return to usual level of functioning at work, home, or school; fourth, feeling in emotional control; fifth, participating in and enjoying relationships with family and friends; and only sixth, absence of symptoms of depression (negative affect). This indeed suggests that patients put a much larger emphasis on positive affect in their expectations.24 The question indeed is whether cure from depression results from a decrease in (negatively defined) anhedonia or from an increase in (positively defined) interest or pleasure? Many clinicians take it for granted that a decrease in negative affect will automatically result in an increase in positive affect, but research shows that the relation between negative and positive affect is more complicated: correlation coefficients between both are reported to be only about –0.3021.

In conclusion, the difference between (normal) sadness and depression, as well as the difference between anhedonia and positive mood or well-being, has a history of reflection, debate, and hesitation, not only in terms of the classification systems, but also in the assessment of outcome in depression. A more careful differentiation between (normal) sadness and depression could probably enhance diagnostic accuracy, and a more careful taking into account of positive affect would probably be beneficial to the depressed patient. ■

References
L’humeur dépressive et l’anhédonie, deux symptômes clés de la dépression majeure telle qu’elle est définie dans le Diagnostic and Statistical Manual of Mental Disorders (DSM), sont plus complexes qu’on ne le pense généralement. Dans la pratique quotidienne, il est cliniquement pertinent de faire la différence entre l’humeur dépressive et la tristesse, et entre l’humeur dépressive et le deuil. La première est davantage un état d’âme ou un état affectif indépendant d’une perte, la seconde une émotion plutôt liée à une perte. La réalité clinique montre cependant que les patients, surtout lors du premier épisode dépressif (moins lors d’une récidive), rapportent volontiers des événements de vie stressants souvent liés à une perte. L’anhédonie, manque d’intérêt ou de plaisir, est un critère composé puisque la perte d’intérêt (anhédonie de motivation ou d’appétence) et la perte de plaisir (anhédonie de consommation) sont des phénomènes différents. Une autre question clinique pertinente est de savoir si l’opposé de l’anhédonie est l’absence d’anhédonie ou bien une humeur positive et un bien-être. Les outils les plus fréquemment utilisés pour évaluer un changement au cours d’un traitement antidépresseur se concentrent davantage sur l’humeur dépressive que sur l’anhédonie. Ceci est inquiétant car très éloigné des attentes des patients en termes de traitement. Des études ont en effet montré que le critère le plus important pour les patients était la restauration d’une santé mentale positive (optimisme, entrain, confiance en soi). Pour conclure, le diagnostic de la dépression pourrait être plus fiable si la différence entre tristesse (normale) et humeur dépressive était plus rigoureusement établie, et le patient dépressif bénéficierait d’une meilleure prise en compte d’une humeur positive.
Pleasure and depression: anhedonia as a core feature

by M. Di Giannantonio, Italy

Anhedonia is a condition in which the capacity to experience pleasure is totally or partially lost. Although anhedonia is a feature of major depressive disorder according to the diagnostic criteria for major depression in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, to date it has received relatively little attention in terms of clinical research. In the past, however, anhedonia has played an important role in theories of psychopathology. In this paper, we review anhedonia by starting with the different historical conceptualizations of pleasure, which have both practical and theoretical implications for the analysis of anhedonia. Anhedonia can refer both to a state symptom in various psychiatric disorders and a personality trait. The main methods utilized to investigate and assess anhedonia (or hedonic capacity) are presented. The neural system underlying reward is becoming increasingly well defined in humans, and there are multiple constructs embedded within the concept of pleasure. We review the neurobiology of anhedonia that reflects the deficits in hedonic capacity. Currently, there is no definitive specific pharmacological approach to the treatment of anhedonia in depression. Preliminary findings have described the efficacy of agomelatine in the treatment of anhedonia, and the effect of agomelatine on anhedonia may be a novel property among antidepressant agents, warranting further investigation. The efficacy of agomelatine on this dimension may hold particular importance for the treatment of patients with major depression.

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Anhedonia played an important role in theories relating to psychopathology at the beginning of the 20th century.\(^3\) For Kraepelin, loss of pleasure and interest and the annihilation of emotional activity were aspects of his wider concept of “indifference.”\(^4\) He spoke about anhedonia as a core symptom of a state of individual suffering that was a part of dementia praecox. Kraepelin described his patients as not feeling any real joy in life; according to him, the characteristic indifference of patients toward social interactions that would previously elicit emotion, the extinction of affection for family and friends, and the loss of satisfaction in their work and vocation and in recreation and pleasure were rather often the first symptoms to manifest, marking the onset of the disease. Bleuler, noting the indifference that some patients exhibited toward their friends, acquaintances, and colleagues, and toward life itself, defined anhedonia as a basic feature of their disease, “an external signal of their pathological condition.”\(^5\) What emerges when reading the works of Kraepelin and Bleuler is that they fundamentally interpreted the loss of the pleasure experience as only one facet of the deterioration of the patient’s emotional life. After the turn of the century, however, psychiatric interest in anhedonia faded, and Jaspers in his “Allgemeine Psychopathologie” does not mention it, considering loss of pleasure to be part of “apathy.”\(^6\)

As far back as the original Feighner criteria published in 1972, anhedonia has, however, been presumed to be a core feature of major depressive disorder (MDD),\(^7\) and Klein’s concept in the 1970s of endogenomorphic depression revived interest in the notion of anhedonia.\(^8\) Klein’s definition of anhedonia was that of “a sharp, unreactive, pervasive impairment of the capacity to experience pleasure, or to respond affectively to the anticipation of pleasure.” From the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) onward, anhedonia has been considered a core symptom of major depression separate from depressed mood.\(^9\) Moreover, it is a necessary symptom for a diagnosis of depression with melancholic features. In 1992, anhedonia entered the lexicon of the International Classification of Diseases. The DSM (Fourth Edition, Text Revision; DSM-IV-TR) defines anhedonia as diminished interest or pleasure in response to stimuli that were previously perceived as rewarding during a premorbid state.\(^10\)

Recent reports estimate that approximately 37% of patients with MDD experience clinically significant anhedonia.\(^11\) Compared with MDD patients without anhedonia, MDD patients with anhedonia have been found to demonstrate greater social impairment, have higher scores on measures of depression and hopelessness, be less neurotic, be younger, and be more often female than male.\(^12\) There is also evidence to suggest a correlation between anhedonia and psychomotor retardation among adults with MDD. Different studies have found that anhedonia can precede the onset of a depressive episode\(^13\) and is a common residual symptom after treatment.\(^14\)

- **Anhedonia by type:**
  - Generalized anhedonia
  - Social anhedonia
  - Physical anhedonia

- **Anhedonia by psychiatric disorder:**
  - Psychotic anhedonia
  - Depressive anhedonia
  - Anhedonia in eating disorders
  - Anhedonia in alcohol and substance abuse
  - Anhedonia in Parkinson disease

### Table I. Classification of various types of anhedonia.

The term anhedonia can refer both to a state symptom in various psychiatric disorders and a personality trait.\(^16\) For example, anhedonia is one of the negative symptoms of schizophrenia. There are, however, important differences between the anhedonic symptoms in mood disorders and those in schizophrenia as regards time course and degree of insight. Anhedonia has also been linked to anxiety and adjustment disorders,\(^17\) suicidal ideation,\(^18\) successful suicide,\(^19\) and Parkinson disease.\(^20\) Moreover, in various disorders and dysfunctional behaviors such as overeating and eating disorders in general,\(^21\) alcohol and substance abuse,\(^22\) and impulse control disorders,\(^23\) anhedonia is often considered to be a prodromal state (Table I).

**Selected Abbreviations and Acronyms**

- 5-HT\(_{2C}\): serotonin 2C
- BDNF: brain-derived neurotrophic factor
- BRMS: Bech-Rafaelsen Melancholia Scale
- CGI: Clinical Global Impression Scale
- DA: dopamine
- DSM: Diagnostic and Statistical Manual of Mental Disorders
- FCPS: Fawcett-Clark Pleasure Scale
- HAM-A: Hamilton Anxiety Scale
- HAM-D: Hamilton Depression Rating Scale
- MADRS: Montgomery-Asberg Depression Rating Scale
- MDD: major depressive disorder
- MRPES: Mood-Related Pleasant Events Schedule
- NAcc: nucleus accumbens
- OFC: orbitofrontal cortex
- PAORS: Pleasurable Activity Observer Rating Scale
- PAS: Physical Anhedonia Scale
- PASRS: Pleasurable Activity Self-Rating Scale
- PES: Pleasant Events Schedule
- RSS: Reinforcement Survey Schedule
- SANS: Scale for the Assessment of Negative Symptoms
- SAS: Social Anhedonia Scale
- SHAPS: Snaith-Hamilton Pleasure Scale
- SSRI: selective serotonin reuptake inhibitor
- TEPS: Temporal Experience of Pleasure Scale
- VAS: visual analog scale
Diagnosing anhedonia
The limited attention that anhedonia has received to date in terms of clinical research could, in part, be the result of the low availability of short, well-validated, and easy-to-use tools for its assessment and investigation.24

There are two methods that are utilized the majority of the time to investigate and assess anhedonia (or hedonic capacity): laboratory-based measures and rating scales. The first approach involves signal-detection methodology, physiological measures, and subjective hedonic response to pleasant stimuli. Besides these behavioral measures, anhedonia can also be evaluated using hemodynamic and electrophysiological measures. The second approach is primarily diagnostic and involves the use of questionnaires. Anhedonia forms the subject of a subsection of questions on certain popular rating instruments like the Bech-Rafaelsen Melancholia Scale (BRMSS), used in depression evaluation, and the Scale for the Assessment of Negative Symptoms (SANS), used in schizophrenia evaluation. The first attempts to assess anhedonia alone go back to the end of the 1960s, with the Reinforcement Survey Schedule (RSS) and the Pleasant Events Schedule (PES). Since then, many researchers have attempted to operationalize the concept, and several scales have been developed to assess anhedonia or hedonic capacity. Specific scales in use for the measurement of anhedonia are: the Physical and Social Anhedonia Scales (PAS and SAS, respectively), self-administered tests that consider anhedonia above all as a trait; the Fawcett-Clark Pleasure Scale (FCPS), a 36-item scale in which subjects have to imagine potentially rewarding situations; the two scales developed by Brown and colleagues, one self-administered (Pleasurable Activity Self-Rating Scale [PASRS]) and the other administered by an observer (Pleasurable Activity Observer Rating Scale [PAORS]); the Mood-Related Pleasant Events Schedule (MRPES), derived from the PES; and the Snaith-Hamilton Pleasure Scale (SHAPS).

Furthermore, it is worth mentioning the 10-cm visual analog scale (VAS) for pleasure and the Temporal Experience of Pleasure Scale (TEPS), which was developed to assess anticipatory and consummatory pleasure.

Of these scales, the one that has been used most in the past few years is SHAPS,27 a 14-item self-report questionnaire designed to measure hedonic tone. SHAPS has shown adequate overall psychometric properties in clinical and student samples, and was found to be highly reliable in terms of internal consistency and test-retest stability. Its discriminant validity has been supported by its lack of association with items related to depressed mood and anxiety on the Montgomery-Asberg Depression Rating Scale (MADRS).28 Furthermore, SHAPS has been found to correlate in a theoretically meaningful way with other measures of affect and personality. Patients with depression, psychosis, or substance dependence scored significantly higher on SHAPS than healthy controls, while patients with depression displayed the highest SHAPS score. The items on SHAPS cover four domains of hedonic experience: interest/pastimes, social interaction, sensory experience, and food/drink. SHAPS instructs participants to agree or disagree with statements of hedonic response in pleasurable situations. Four responses are possible: strongly disagree, disagree, agree, or strongly agree. If the subject answers “strongly agree” or “agree,” the item is assigned a score of zero, while for “disagree” or “strongly disagree,” the score is 1. A total score can be derived by summing the scores for the answers to each item, thereby producing a total score ranging from 0 (absence of anhedonia) to 14 (complete anhedonia). Thus, higher SHAPS total scores indicate greater anhedonia, and a score of 3 or more indicates a significant reduction in hedonic capacity and seems to discriminate between healthy and clinically depressed patients. Participants completing SHAPS are instructed to respond on the basis of their ability to experience pleasure “in the last few days.”

Neurobiology of pleasure and anhedonia
The neural system underlying reward is quite well defined in animals and humans: the euphoric response to dextroamphetamine, cocain-induced euphoria, monetary reward, and even pleasurable responses to music, pictures, and attractive faces have all been associated with activity within the nucleus accumbens (NAcc), ventral caudate, and ventral putamen.26 More specifically, release of dopamine (DA) within the ventral striatum may be involved in the anticipation and generation of motor responses associated with future rewards, the so-called “wanting.”27 On the other hand, the main mediators of pleasurable hedonic experience (“liking”) appear to be the endogenous opioids, particularly in the shell of the NAcc and the ventral pallidum.28 The orbitofrontal cortex (OFC) and anterior cingulate cortex also play important roles in the neural reward system. The former is implicated in the subjective representation of incentive salience, hedonic impact, and hedonic experience; the latter is primarily involved in evaluating the costs and benefits of a given set of options.29 Finally, other cerebral structures such as the amygdala are also involved in the reward system, as are neurotransmitters such as serotonin and γ-aminobutyric acid (GABA). Serotonin, for example, has a recognized effect on the modulation of DA and opioid release: serotonin reuptake inhibitors raise the threshold for brain stimulation reward and reduce the firing rate of DA neurons in the ventral tegmental area.30 L-3,4-dihydroxyphenylalanine (l-DOPA) alterations in the striatum are present in depressed individuals with flat affect or psychomotor slowing, but not in depressed individuals without these symptoms.31 One study restricted to patients with MDD and anhedonic symptoms reported decreased DA transport binding in the striatum.32 Data supporting a role of DA in MDD come from studies of DA turnover, in which it has been observed that individuals with MDD have decreased cerebrospinal fluid levels of homovanillic acid, the primary metabolite of DA.28 These studies suggest the presence of a reduced
basal dopaminergic tone in MDD. Additionally, pharmacological interventions that block or deplete DA can induce or deepen depressive symptoms in currently depressed or remitted individuals, further implicating DA dysfunction in MDD. Moreover, in animal models of depression, several lines of evidence support the role of DA dysfunction. Studies investigating the effects of a deficient endogenous opioid system in depression and anhedonia have by contrast produced largely equivocal findings, and to date, no studies have specifically evaluated opioid systems in reward liking or other aspects of reward processing in MDD patients. In MDD, both the OFC and the anterior cingulate cortex have shown a variety of alterations in gross morphology, neuronal structure, function, connectivity, and neurochemistry.

Despite it having been shown in the 1970s that the presence of anhedonia is predictive of antidepressant response, studies in the current literature often neglect to assess anhedonia in the evaluation of antidepressant response, and efficacy data on this specific dimension are sparse. Boyer showed a late effect of sertraline on anhedonia (over 21 to 56 days), which occurred after its effects on depression and anxiety, while in a study by Tomarken, the catecholaminergic effects of bupropion SR 300 tended to produce more robust effects than placebo on anhedonia/positive affect, particularly during a 6-week initial treatment phase.

However, for many authors, anhedonia is considered a particularly difficult symptom to treat, as accruing evidence suggests that current first-line pharmacotherapies (eg, selective serotonin reuptake inhibitors [SSRIs]) do not adequately address motivational and reward-processing deficits in depression. Indeed, their ability to improve diminished positive affect by relieving symptoms of low energy, decreased motivation, and anhedonia has been questioned. A related issue is that some patients associate their SSRI treatment with an experience of emotional blunting, whereby emotional responses to both aversive and pleasurable experiences are diminished. Thus, increases in serotonin function produced by SSRIs could produce a form of “emotional constraint” in which the salience of both rewarding and aversive stimuli is lost. Considering the widespread use of SSRIs, such an effect could have considerable personal, clinical, and social implications, and the presence of anhedonic symptoms is considered a predictor of poor treatment response. Moreover, investigating the effect of SSRIs on emotional responses in depressed patients is difficult, because loss of pleasure may persist even during clinical remission. In addition, modest degrees of emotional blunting might be difficult for individuals to subjectively detect or report.

Agomelatine (S20098, N-[2-(7-methoxynaphth-1-yl)ethyl]acetamide) has a novel neurochemical mechanism that is unlike that of other antidepressants. It is an MT1 and MT2 melatonergic receptor agonist and a selective antagonist of the 5-HT2C receptor.
rapidly relieves symptoms compared with placebo. In addition, levitates symptoms of anxiety associated with depression, and suggests that agomelatine has antidepressant properties, rated to test the possible use of agomelatine in the treatment of serotonin.

Evidence from preclinical and clinical studies showed that agomelatine was associated with early clinical improvement, this study also provided evidence of an early response (first week of treatment) and improvement in depression scores following an increase in the agomelatine dose, with a good tolerability profile (Table II).

Moreover, agomelatine was shown to be efficacious in the treatment of anhedonia. A reduction of 1.6 points from baseline was observed on SHAPS after the first week of treatment ($P<0.05$), with the reduction increasing at different time points until the end of the trial, whereupon the level of significance was even greater ($P<0.01$).

In the second study, the effects of agomelatine on anhedonia were compared with those of venlafaxine XR. In this open-label, 8-week parallel-group pilot study, patients with MDD were randomly started on either agomelatine at a dose of 25-50 mg/day (n=30) or venlafaxine XR at a dose of 75-150 mg/day (n=30). Treatment outcomes in terms of improvement in anhedonia (SHAPS), depression, and anxiety scores (HAM-D; HAM-A) were assessed after 1 (T1), 2 (T2), and 8 (T3) weeks. A significant reduction over time was observed in SHAPS scores in both the agomelatine (F=20.74; $P<0.001$) and the venlafaxine XR (F=3.27; $P<0.5$) groups. However, there was a significant difference between groups in favor of agomelatine at T1 ($P<0.05$), T2 ($P<0.01$), and T3 ($P<0.01$), with the number needed to treat being 8 subjects in favor of agomelatine in terms of the presence or absence of an anhedonic state (SHAPS $\geq 3$) at study end (Figure 2).

A significant reduction in HAM-D and HAM-A scores was observed for both groups ($P<0.05$), with no difference between groups, but only open-label 8-week study, included 30 male and female outpatients aged 18 to 60 years old, with a DSM-IV diagnosis of MDD. The primary end points were reduction in depressive and anxiety symptoms, expressed by the scores on the Hamilton Depression and Anxiety Rating Scales (HAM-D; HAM-A). The secondary end points were related to the reduction in the degree of anhedonia and insomnia. In this open-label study, agomelatine was shown to be a possible therapeutic option for patients with MDD. In line with previous studies in which agomelatine was associated with early clinical improvement, this study also provided evidence of an early response (first week of treatment) and improvement in depression scores following an increase in the agomelatine dose, with a good tolerability profile (Table II).

Given its novel neurochemical mechanism, the antidepressant activity of agomelatine may have different and specific effects on the broad range of symptoms usually observed in a depressive syndrome. The specific effect of circadian rhythm resynchronization may contribute to the regulation of hedonic capacity. In view of the latter, a line of studies was inaugurated to test the possible use of agomelatine in the treatment of anhedonia. Two studies have described the efficacy of agomelatine in the treatment of anhedonia. The first, an open-label 8-week study, included 30 male and female outpatients aged 18 to 60 years old, with a DSM-IV diagnosis of MDD. The primary end points were reduction in depressive and anxiety symptoms, expressed by the scores on the Hamilton Depression and Anxiety Rating Scales (HAM-D; HAM-A). The secondary end points were related to the reduction in the degree of anhedonia and insomnia. In this open-label study, agomelatine was shown to be a possible therapeutic option for patients with MDD. In line with previous studies in which agomelatine was associated with early clinical improvement, this study also provided evidence of an early response (first week of treatment) and improvement in depression scores following an increase in the agomelatine dose, with a good tolerability profile (Table II).

Moreover, agomelatine was shown to be efficacious in the treatment of anhedonia. A reduction of 1.6 points from baseline was observed on SHAPS after the first week of treatment ($P<0.05$), with the reduction increasing at different time points until the end of the trial, whereupon the level of significance was even greater ($P<0.01$).

In the second study, the effects of agomelatine on anhedonia were compared with those of venlafaxine XR. In this open-label, 8-week parallel-group pilot study, patients with MDD were randomly started on either agomelatine at a dose of 25-50 mg/day (n=30) or venlafaxine XR at a dose of 75-150 mg/day (n=30). Treatment outcomes in terms of improvement in anhedonia (SHAPS), depression, and anxiety scores (HAM-D; HAM-A) were assessed after 1 (T1), 2 (T2), and 8 (T3) weeks. A significant reduction over time was observed in SHAPS scores in both the agomelatine (F=20.74; $P<0.001$) and the venlafaxine XR (F=3.27; $P<0.5$) groups. However, there was a significant difference between groups in favor of agomelatine at T1 ($P<0.05$), T2 ($P<0.01$), and T3 ($P<0.01$), with the number needed to treat being 8 subjects in favor of agomelatine in terms of the presence or absence of an anhedonic state (SHAPS $\geq 3$) at study end (Figure 2).

A significant reduction in HAM-D and HAM-A scores was observed for both groups ($P<0.05$), with no difference between groups, but only

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**Table II. Agomelatine efficacy in the various dimensions of depression.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Outcome measure</th>
<th>Baseline</th>
<th>Week 8</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms</td>
<td>HAM-D</td>
<td>26.5±3.7</td>
<td>12.2±6.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety symptoms</td>
<td>HAM-A</td>
<td>22.4±4.8</td>
<td>11.2±5.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>SHAPS</td>
<td>4.4±6.2</td>
<td>2.1±6.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Sleep</td>
<td>LSEQ</td>
<td>35.9±7.3</td>
<td>48.5±2.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Quality of life</td>
<td>QOL</td>
<td>2.1±0.8</td>
<td>4.7±0.6</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Figure 2.** Agomelatine versus venlafaxine in treating anhedonia.

**Abbreviations:** HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Rating Scale; SHAPS, Snaith-Hamilton Pleasure Scale.

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**Sharon Aguiar**

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**References:**


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**Sharon Aguiar**
patients who were treated with agomelatine showed a statistically significant improvement in scores on the Clinical Global Impression (CGI) scale \( t(=2.94); P<0.05 \). Improvements in anhedonia scores were detected as early as 1 week after treatment initiation with agomelatine, which was a beneficial characteristic, especially given the usually relatively slow onset of antidepressant efficacy with current agents. In both of these studies, use of agomelatine did not determine the onset of hypomanic or manic symptoms.\textsuperscript{12}

The results of these two studies need to be interpreted with caution due to some limitations. First, the small sample size does not allow for firm conclusions to be drawn. Second, the absence of a placebo group and the open design are weaknesses that temper the interpretation of the results. The results regarding agomelatine and anhedonia are difficult to compare with those from other clinical studies, as anhedonia is a dimension that has been poorly characterized in all the major clinical trials involving treatment of MDD.

**Conclusion**

Different studies have found that anhedonia can precede the onset of a depressive episode,\textsuperscript{14} influence its severity, and predict poor outcome 12 months later.\textsuperscript{46} Moreover, anhedonia is considered to be a common residual symptom after treatment\textsuperscript{11} and is associated with dysfunction in the brain reward system.\textsuperscript{46}

The limited attention that anhedonia has so far received in terms of clinical research could be the main explanation for the fact that there is currently no definitive specific pharmacological approach to the treatment of anhedonia in depression. Anhedonia has been poorly characterized in all the major clinical trials involving treatment of MDD, where it has only been considered as one of a large range of symptoms, despite being one of the two core symptoms of major depression. Anhedonia warrants further study, as an important issue concerns whether patients with anhedonia have a different pattern of symptoms to patients without anhedonia: such differential symptom expression could have important implications with respect to the etiology of MDD and its prevention and treatment. Differentiating patients into subtypes in line with their symptom typology and the phenomenological approach may represent the future of psychopharmacology, resulting in the right choice of antidepressant for the specific symptom(s). Given its novel neurochemical mechanism, the antidepressant activity of agomelatine may have different specific effects on the broad range of symptoms usually observed in a depressive syndrome, and the specific effect of circadian rhythm re-synchronization may contribute to the regulation of hedonic capacity. The original effect of agomelatine on anhedonia is a novel property among antidepressant agents and may hold particular importance for the treatment of patients with major depression: it thus deserves further investigation with larger samples and double-blind, placebo-controlled designs.\textsuperscript{18}

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Keywords: agomelatine; anhedonia; depression; pleasure; SHAPS

**PLAISIR ET DÉPRESSION : L’ANHÉDONIE, UN SYMPTÔME CLÉ**

L’anhedonie est un état dans lequel l’aptitude à éprouver du plaisir est totalement ou partiellement perdue. Bien qu’étant caractéristique de l’épisode dépressif majeur selon le critère diagnostique de la dépression majeure dans la quatrième édition du Diagnostic and Statistical Manual of Mental Disorders, la recherche clinique s’y est, à ce jour, relativement peu intéressée. Jadis cependant, l’anhedonie a joué un rôle important dans les théories de la psychopathologie. Dans cet article, nous étudions l’anhedonie en commençant par les différentes théories historiques du plaisir, dont les implications sont à la fois pratiques et théoriques. L’anhedonie peut se référer à un symptôme particulier dans plusieurs troubles psychiatriques ou à un trait de personnalité. Nous présentons les principales méthodes utilisées pour rechercher et évaluer l’anhedonie (ou capacité hédonique). Le système neural de la récompense est de mieux en mieux compris chez les humains, et de nombreuses idées sont ancrées dans le concept de plaisir. Nous analysons la neurobiologie de l’anhedonie qui reflète le déficit de la capacité hédonique. Il n’existe pas actuellement d’approche pharmacologique spécifique du traitement de l’anhedonie dans la dépression. L’efficacité de l’agomélatine dans le traitement de l’anhedonie a été prouvée par des résultats préliminaires, et cet effet pourrait être une nouvelle propriété des antidépresseurs, justifiant des recherches plus poussées. L’efficacité de l’agomélatine sur l’anhedonie peut revêtir une importance particulière pour le traitement des patients atteints de dépression majeure.
Anxiety in depression: clinical and conceptual considerations

by D. J. Stein, South Africa

It is increasingly accepted that anxiety in depression is associated with increased morbidity, that anxiety disorders typically precede the development of major depression, and that patients with major depression and anxiety respond to efficacious treatments and so deserve early and robust intervention. However, the occurrence of anxiety in depression raises many complex questions: Should the co-occurrence of depression and anxiety be conceptualized as a comorbidity or as a separate diagnostic construct? Does anxiety in depression have particular psychobiological correlates and deserve distinctive treatments? What are the implications of co-occurring anxiety for understanding the nature of depression? This review emphasizes that both categorical and dimensional approaches to co-occurring depression and anxiety are needed, that anxiety in depression is a heterogeneous construct, and that variants of anxious depression, such as stressor-related depression and agitated depression, likely require quite different approaches.

The topic of anxiety in depression is, on the one hand, a reasonably straightforward one. The literature emphasizes a number of clinically important lessons: anxiety is a potentially important symptom of major depression that is associated with increased morbidity; anxiety disorders typically precede the development of major depression; and patients with major depression and anxiety respond to efficacious treatments and, therefore, deserve early and robust intervention.

On the other hand, the occurrence of anxiety in depression raises many complex questions: Should the co-occurrence of depression and anxiety be conceptualized as a comorbidity or as a separate diagnostic construct? Does anxiety in depression have particular psychobiological correlates and, therefore, deserve distinctive treatments? Is anxiety in depression merely a clinical observation, or can this co-occurrence shed light on some deeper questions about our understanding of the nature and experience of depression?

Here, I will briefly review some of the clinically important lessons that the literature has provided on anxiety in major depression, but also address some of the more complex conceptual issues in this area in an attempt to outline some clinically relevant approaches to these debates. I will briefly address in turn the phenomenology, psychobiology, and management of anxiety in major depression.

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Phenomenology of depression-anxiety comorbidity

It has long been recognized that anxiety is a central clinical feature of major depression. Anxiety is a prevalent symptom in depression, and patients with anxious depression have greater morbidity, as assessed by a number of indices, including symptom severity, illness chronicity, functional impairment, and suicide risk.2,3 Indeed, participants in both depression and several anxiety disorders are used. Given such overlaps, an immediate nosological question is whether co-occurrence of depression and anxiety represents an artifact of the diagnostic system?2,3 Indeed, it has been suggested that mixed anxiety-depressive disorder, characterized by subthreshold depressive and anxiety symptoms, is highly prevalent and disabling, and therefore deserves recognition as an independent diagnostic entity.4 This disorder is listed in the appendix of the DSM, Fourth Edition (DSM-IV), and is widely employed when International Classification of Diseases, Tenth Revision (ICD-10) diagnoses are used.

Such a view may be supported by many who work in primary care settings. Mixed presentations of depressive and anxiety symptoms are common in these settings, and practitioners who have relatively little time to undertake detailed assessments may argue that an encompassing entity (ie, mixed anxiety-depressive disorder) facilitates efficient diagnosis and treatment planning.5 Certainly, a number of antidepressants are currently considered first-line agents for the treatment both of major depression and anxiety disorders.10

### Table I. Overlap in symptoms of depression and anxiety

<table>
<thead>
<tr>
<th>Depression</th>
<th>Overlap</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood, anhedonia</td>
<td>Irritability, apprehension/panic</td>
<td>Hypervigilance, startle response</td>
</tr>
<tr>
<td>Ruminations about past/guilt/dying</td>
<td>Negative rumination/worry</td>
<td>Worried about future</td>
</tr>
<tr>
<td>Loss of interest</td>
<td>Social withdrawal, distress, dysfunction</td>
<td>Agoraphobia</td>
</tr>
<tr>
<td>Retardation</td>
<td>Agitation</td>
<td>Muscle tension</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Weight gain/loss</td>
<td>Gastrointestinal complaints</td>
<td>Chronic pain, decreased concentration, fatigue</td>
</tr>
</tbody>
</table>

On the other hand, it is also important to recognize that anxiety disorders are the most prevalent psychiatric disorders, and that they are underdiagnosed and undertreated. Thus, a contrary view is that epidemiological data on mixed anxiety-depressive disorder have significant methodological limitations, and that in patients with both depressive and anxiety symptoms, it is crucial to determine if a particular anxiety disorder is currently present or will develop over time.11 There are important differences in the management of different anxiety disorders, so these need carefully tailored assessment and intervention.

A potential compromise here is to recognize the importance of both categorical and dimensional approaches to psychiatric disorders in general, and to depression and anxiety in particular.12,13 Separate diagnostic categories for different mood and anxiety disorders have been useful in ensuring efficient clinical communication, and also in preliminary neurobiological research. At the same time, the use of dimensional assessments of anxiety in major depression may be useful in emphasizing the spectrum of anxiety symptoms seen in depression, and in encouraging researchers and clinicians to evaluate this set of symptoms more rigorously.

### Psychobiology of depression-anxiety comorbidity

It has long been recognized that anxiety in major depression is associated with significantly worse treatment outcome.14,15 The recent STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression) similarly found that anxious depression is associated with lower response and remission rates, as well as slower response, than nonanxious depression, with a poorer response not only to first-line antidepressant treatment, but...
also after second-line switching and augmentation pharmacotherapy or psychotherapy. Furthermore, patients with anxious depression had increased side-effect frequency, intensity, and burden.

It is also important to emphasize that anxiety disorders typically precede the onset of major depression. It is notable that an animal literature has emphasized that after maternal separation, there is first a separation anxiety response, and subsequently a despair response. Along these lines, an early neurobiological explanation suggested initial involvement of the GABAergic system in anxiety, with subsequent dysregulation of monoamine neurotransmitters in major depression. Ultimately, however, the relevant mechanisms which mediate the temporal sequence from anxiety to depression remain poorly delineated.

Indeed, it is far from clear that anxious depression is characterized by specific neurocircuitry alterations, or by a particular neurochemical or neurogenetic signature. The STAR*D authors conceded that as anxious depression was associated with greater severity of depression, lower socioeconomic status, and higher physical illness burden, anxious depression may not represent a different depression subtype. While participants at a recent DSM-5 conference agreed that depression and GAD are different disorders, there was also a view that the relevant neurobiological data in this area are hardly conclusive. Clearly, much further psychobiological research is needed. Still, even with future advances, biomarkers will not necessarily be able to carve nature at her joints. Nesse and colleagues have emphasized, for example, that there may be many routes by which genetic variations could influence vulnerability to mood and anxiety disorders, including preference for alcohol or for very exciting mates, a tendency to persist in pursuing a life goal even when there is no chance of success, or anxiety that impedes making a needed major life change. Thus, we should not be looking only for a few genes specific for, say, co-occurrence of major depression and anxiety, but rather for many genes that influence risk via multiple overlapping pathways.

One useful approach to the psychobiology of anxious depression may be to pay greater attention to the effects of anxiety on key psychological processes in depression. There has been increased attention recently, for example, to disturbances in emotion regulation in several psychiatric disorders, including mood and anxiety disorders. Anxious depression may be associated with particular kinds of cognitive distortion and with increased avoidance strategies. Such processes may have certain psychobiological correlates; for example, corticolimbic circuitry mediates reappraisal and suppression. Furthermore, such processes might then be targeted during treatment. Along complementary lines, Nesse has argued that there is a need to consider subtypes of disorders based not only on neurocircuitry and genotype findings, but on a deeper understanding of the functions of the underlying motivational systems. The profound overlap between anxiety and depression may arise because they are responses to related kinds of danger; a threat that creates anxiety may lead to an actual loss that precipitates depression. This kind of evolutionary explanation is important in supplementing proximate explanations (focused on underlying psychobiological mechanisms) with distal explanations (focused on evolved adaptive responses).

Management of depression-anxiety comorbidity

It seems clear that patients with major depression and anxiety symptoms deserve early and robust intervention. Multiple studies with multiple antidepressants have indicated that these agents are efficacious and well tolerated in the treatment of patients with major depression with co-occurring anxiety symptoms. Given that anxiety symptoms in depression are an important prognostic indicator, patients with such symptoms need to be evaluated carefully and treated appropriately.

While it is very difficult to demonstrate conclusively that early treatment of anxiety disorders is effective for decreasing the development of subsequent comorbid depression, there are some data which point in this direction. It would seem entirely reasonable to encourage the early detection and management of anxiety disorders in order to help prevent the subsequent onset of comorbid major depression, substance use disorders, and other negative outcomes.

An immediate question, however, is whether co-occurrence of depression and anxiety deserves a unique treatment? The presence of unique biological markers would certainly encourage that interventions address the relevant targets. The lack of such markers is consistent with the opinion that no specific pharmacotherapeutic intervention has yet proven distinctively superior in the treatment of anxious depression. That said, it is noteworthy that there may be a modest advantage for selective serotonin reuptake inhibitors (SSRIs) over bupropion, and of agomelatine over SSRIs, in the treatment of anxious depression.

Work on the management of anxious depression raises the key question of why anxiety is so often overlooked in the management of depression. A key clinical lesson may emerge from a deeper consideration of the experience of depression; we have a tendency to think of depression as a “down,” and to use language consistent with this metaphor (eg, low mood, low energy). This in turn may make it hard to recognize such conditions as bipolar disorder (with its phases of mania) and more agitated depressions (where anxiety plays a key role). This failure to recognize the full spectrum of the experience of depression can have significant negative consequences; in
particular, clinicians may underestimate the severity of anxious depression and its clear link with negative outcomes such as suicide.

Perhaps a second clinical lesson emerges from literature which emphasizes the heterogeneity of anxious depression, and the importance of understanding the context of the relevant symptoms. Ghaemi, for example, has emphasized the neglect of the old concept of “neurotic depression,” a form of depression in which there is increased anxiety, often in response to life stressors. Similarly, Nesse has emphasized mood, rather than as major depression.

In contrast, anxiety respond to efficacious treatments and so deserve early and robust intervention. However, the occurrence of anxiety in depression raises many complex questions. This review emphasizes that both categorical and dimensional approaches to co-occurring depression and anxiety are needed, that anxiety in depression is a heterogeneous construct, and that variants of anxious depression, such as stressor-related depression and agitated depression, likely require quite different approaches.

References

Emotions and depression

Anxiety in depression: clinical and conceptual considerations – Stein


Keywords: anxiety; comorbidity; co-occurrence; depression; diagnostic categories; DSM-5; management; phenomenology; psychobiology

Les symptômes de l’anxiété dans la dépression : considérations cliniques et conceptuelles

Il est de plus en plus reconnu que l’anxiété dans la dépression est associée à une morbidité augmentée, que les troubles anxieux précèdent de façon typique l’apparition d’une dépression majeure et que les patients souffrant d’une dépression majeure et d’anxiété, répondant aux traitements efficaces, méritent d’être pris en charge de façon précoce et énergique. Des questions complexes sont néanmoins soulevées par la survenu de l’anxiété dans la dépression : la coexistence d’une dépression et d’une anxiété doit-elle être considérée comme une comorbidité ou bien comme deux diagnostics séparés ? L’anxiété dans la dépression a-t-elle des corrélats psychobiologiques particuliers justifiant de traitements spécifiques ? Qu’apporte l’apparition d’une anxiété dans la compréhension de la nature de la dépression ? Cet article souligne la nécessité d’une approche à la fois dimensionnelle et catégorielle de la coexistence dépression-anxiété, l’hétérogénéité de l’entité « anxiété dans la dépression » et le besoin probable d’approches différentes pour les variantes de dépression anxieuse, comme la dépression liée au stress et la dépression agitée.
Antidepressants and emotions: therapeutics and iatrogenic effects

by H. J. Möller and F. Seemüller, Germany

Antidepressants can ameliorate depressive symptoms. Apart from the specific pharmacological action of the respective compound, we still have little knowledge about the way antidepressant drugs modulate neural processing of emotional and affective information. One proposed mechanism is an antidepressant-induced increase in processing of positive information in healthy volunteers and acutely depressed patients early in treatment. Such action may help explain the role of monoamines in emotional dysfunction in depression and how antidepressants work. This article will first provide an overview of pathomechanisms of emotional processing in depression and then review data on emotional processing of serotonergic and noradrenergic compounds. It has also been speculated that antidepressants may, in the same manner that they have positive effects on depression, lead to unwanted secondary emotional effects. Some early case reports suggested that selective serotonin reuptake inhibitors, especially, may lead to emotional blunting, a term commonly referred to as a restricted range of emotions. In the years that followed, this side effect was systematically studied. Relevant articles have been critically reviewed and are summarized in the manner of a systematic review. This article will also discuss the neurobiological underpinnings and possible clinical implications of emotional blunting.

Medicographia. 2013;35:304-309 (see French abstract on page 309)
fun. This may explain why remitted patients are still vulnerable to development of further depressive episodes.\(^2\) Antidepressants seem to affect the way in which emotional information is processed, finally leading to a reduced negative bias in perception and memory that are believed to contribute to the symptoms of depression. Antidepressants may, therefore, work in a manner quite similar to that of psychological treatment that aims to redress negative biases in information processing. Given the possibility that antidepressants—especially selective serotonin reuptake inhibitors (SSRIs)—may neutralize the processing both of negative and positive emotions, one might speculate that such an iatrogenic effect could also blunt subjective response in patients who take them.

In the early nineties, some case reports described a new dimension of side effects which were described as blunted emotional behavior.\(^4,5\) The term blunted emotion is commonly referred to as a restricted range of emotions.

Blunted emotions are also commonly thought to be one of the main obstacles in combining pharmacologic SSRIs with psychotherapy. For example, some psychotherapists recommend cessation of antidepressant SSRIs before exposure therapy in anxiety patients. The rationale behind this is that exposure treatment, in theory, can only be effective if emotions, including anxiety, are not suppressed or blunted by drugs. Consequently, antidepressants are sometimes tapered down or stopped, which is unfortunate, taking into account the significant risk of a recurrence or relapse of the depressive episode.

However, the question remains unanswered whether such side effects really exist or whether they, for example, only represent residual symptoms of the major depressive disorder, such as affective rigidity, or whether they represent personality traits. Recently, with the growing database on side effects of antidepressants, some treatment-emergent emotional side effects for tricyclic antidepressants (TCAs), such as sudden appearance of “anger” and “outburst,” have been described. This article will review the therapeutic effects of serotonergic and adrenergic antidepressants on emotional processing on the one hand, and summarize what is known about the concept of “emotional blunting” on the other, and will, finally, briefly comment on the clinical management of emotional blunting.

**Therapeutic effects of antidepressants on emotional processing**

The improvement of symptoms on a depression rating scale provides good evidence for the efficacy of an antidepressant. While the actions of antidepressants are well characterized (e.g., serotonin reuptake inhibition) there is only little understanding of how these mechanisms lead to an improvement of symptoms. However, the effects of antidepressants on the modulation of emotional processing might provide a deeper understanding of its psychological mode of action.\(^6\) It also helps us as clinicians to explain to our patients what psychological changes can be expected on an antidepressant medication.

There are many studies of acute and long-term administration of antidepressants in animal models, healthy volunteers, and depressed populations. In the following, we will focus on studies in healthy volunteers and in clinical samples.

For example, a single-dose administration of citalopram helped healthy females to correctly process happy facial expressions and to recognize fear. However, citalopram had no effect on any other negative emotions like sadness, anger, and disgust.\(^7\)

Another electrophysiological study by Kemp investigated the effects of acute serotonergic administration of citalopram on cortical electrophysiological responses to the processing of pleasant and unpleasant visual stimuli. Kemp’s findings suggest that acute serotonergic augmentation with citalopram modulates cortical processing of emotionally valenced stimuli, such that the response to pleasant valence is potentiated, whereas the response to unpleasant valence is suppressed.\(^8\)

With respect to long-term administration of SSRIs, Harmer\(^9,10\) found a reduction in the processing of negative emotional stimuli following a seven-day trial of citalopram at a daily dose of 20 mg. At the end of the seven-day period, healthy subjects showed reduced recognition of negative facial expressions and also an improved memory for positive information. A reversal in fear processing from acute to chronic treatment with SSRIs has also been described in many preclinical anxiety models and clinical anxiety can easily be exacerbated initially with SSRI treatment. It is thus tempting to speculate that the initial increase followed by a final decrease in fear perception may relate to opposing effects on neural substrates involved in fear processing and that these changes may relate to the therapeutic effects of SSRIs in depression and anxiety.\(^11\)

With respect to the noradrenergic effect of a single dose of the compound reboxetine, Harmer and coworkers have conducted several important studies. She examined the effect of re-

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**Selected abbreviations and acronyms**

- 5-HT\(_{2C}\): serotonin 2C
- AES: Apathy Evaluation Scale
- BDI: Beck Depression Inventory
- HAM-D: Hamilton Depression Rating Scale
- LEIS: Lauxes Emotional Intensity Scale
- MADRS: Montgomery-Asberg Depression Rating Scale
- OQuESA: Oxford Questionnaire on the Emotional Side effects of Antidepressants
- SSRIs: selective serotonin reuptake inhibitor
- TCAs: tricyclic antidepressant
boxetine on emotional processing compared with placebo in 24 healthy controls. On three different measures, reboxetine biased perception toward positive rather than negative information in the absence of effects on neurocognitive performance. For example, the facial expression task revealed greater recognition of happy facial emotions after reboxetine compared with placebo, without improvement in cognitive performance.\textsuperscript{15}

The effect of depression on emotional processing and its correction by reboxetine is also nicely illustrated in Figure 1.\textsuperscript{6,8} Harmer and colleagues demonstrate that healthy controls seem to have a positive recall bias regarding the recall of positive adjectives, which cannot be found in depressed subjects. However, after single-dose administration of 4 mg of reboxetine, as compared with placebo, the patients regain the usual “healthy” positive recall bias (Figure 1).\textsuperscript{9}

Another interesting study by Harmer\textsuperscript{13} compared reboxetine or citalopram with placebo over seven days in a double-blind manner in 42 healthy volunteers. Both compounds significantly reduced the recognition of fearful and angry facial expression, which cannot be found in depressed subjects. However, after single-dose administration of 4 mg of reboxetine, as compared with placebo, the patients regain the usual “healthy” positive recall bias (Figure 1).\textsuperscript{9}

Generally speaking, the hypothesis is that correcting emotional bias may lead to an improved homeostatic mood response to experience and that recovery in depression is delayed because of the need for relearning of external contingencies and internal states under more positive emotional bias.\textsuperscript{14} On the other hand, the neutralization of negative emotions might in the long run lead to secondary effects like emotional blunting, which will be critically reviewed in the following paragraph.

\textbf{Iatrogenic, secondary effects of antidepressants on emotions}

In 1990, Hoehn-Saric et al reported apathy, indifference, loss of initiative, and disinhibition in panic disorder and depressed patients on SSRIs.\textsuperscript{5} A bit later, in 1991, Hoehn-Saric reported apathy, indifference, inattention, and perseveration in an obsessive-compulsive patient taking fluoxetine.\textsuperscript{4,15} Subsequently, Oleshansky and Labbate (1996) described rapid improvement of excessive or inappropriate crying without apathy or indifference in depressed patients on SSRI treatment.\textsuperscript{16} Finally, Vinar et al reported that eight depressed women spontaneously cried while watching movie scenes on television over a period of years. This crying disappeared during long-term treatment with SSRIs.

The first systematic case-control study on blunted emotions was a brief report by Opbroek published in 2002.\textsuperscript{16} The authors studied 15 depressed patients in remission, who took three different SSRIs (fluoxetine, paroxetine, and sertraline). They were all recruited from a study of patients reporting SSRI-induced sexual dysfunction. Patients and healthy controls were rated with a newly developed blunt-ed-emotions rating scale (Lauxes Emotional Intensity Scale, LEIS).\textsuperscript{16} About 80% of the 15 SSRI-treated remitted patients reported emotional blunting. The LEIS consists of 17 items. In only two items—work and energy levels—did the authors find no significant difference as compared with the healthy controls. The frequency of patients experiencing diminished emotional response was 93% for sexual interest, 80% for sexual pleasure, 60% for inability to cry, 53% for erotic dreams, 50% for creativity, and 47% for becoming irritated or upset. There was no difference

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Depression} & \textbf{Acute reboxetine} & \textbf{Depression} \\
\hline
\textbf{Negative} & \textbf{Positive} & \textbf{Negative} & \textbf{Positive} \\
\hline
Comparison subjects & Depressed patients, placebo & Depressed patients, reboxetine \\
\hline
\end{tabular}
\caption{Mean numbers of positive and negative self-referent adjectives in a recall task. (A) The effects of depression per se. Comparison for positive stimuli between depressed patients and comparison subjects receiving placebo significant at \(P<0.05\). (B) The acute effect of oral reboxetine (4 mg) or placebo in depressed group only. Comparison for positive stimuli between depressed patients receiving placebo and those receiving reboxetine significant at \(P=0.01\). After reference 9: Harmer et al. Am J Psychiatry, 2009;166(10):1178-1184. © 2009, American Psychiatric Association.}
\end{table}
Measuring emotional blunting
A different approach has been suggested by Barnhart et al.\textsuperscript{20} He introduced the term apathy in the context of SSRI-induced emotional blunting and adopted a definition from Marin et al:\textsuperscript{21} a syndrome in which there is a primary absence of motivation that is not attributable to cognitive impairment, emotional distress, or diminished level of consciousness. However, this approach also lacks specificity regarding side effects of antidepressants, as Marin himself suggested the following possible psychiatric differential diagnoses of apathy: delirium, dementia, abulia, akinesia, despair, and depression.\textsuperscript{22} We would like to suggest including other common psychiatric diagnoses, such as negative symptoms in schizophrenia and chronic residual states as well. However, important longitudinal information, such as the late appearance of apathy during SSRI treatment in the absence of depressive symptoms and diminishing apathy during titration downward may provide more helpful information in distinguishing apathy or emotional blunting as a side effect from depressive residual symptoms.

Rating scales for blunted emotions
Regarding standardized rating scales, there are four instruments for the measurement of SSRI-emergent emotional blunting thus far available: the first is the Marin Apathy Evaluation Scale (AES). However, the scale was developed for an older population and has been used in schizophrenia trials and neurological disorders.\textsuperscript{22} The second is the above-mentioned LEIS, comprising 18 questions, which thus far lacks validity and specificity, as outlined above.\textsuperscript{16} The third is the Bell-Shipman Apathy/Emotional Blunting Questionnaire.\textsuperscript{6,23} In the literature, it is described as “under development,” but up to now there is still no published evidence of its completion. The fourth and perhaps most comprehensive and elaborate questionnaire is the recently published Oxford Questionnaire on the Emotional Side Effects of Antidepressants (OQuESA).\textsuperscript{6,24} It comprises three different sections with 26 self-reported items altogether. It has been tested in a cohort of 207 depressed people: 26\% reported that they did not experience side effects; 16\% reported insignificant emotional side effects, 30\% mild side effects, 23\% moderate, and 6\% severe. Patients with emotional side effects were significantly younger, had a significantly higher Beck Depression Inventory (BDI) score and shorter treatment duration. The association with depressive symptoms raises the possibility that the OQuESA may not be specific for side effects, but might rather capture depressive symptomatology. Moreover, emotional side effects were more common in patients with a shorter treatment duration, which also suggests greater illness activity and acuity and contrasts with findings from case reports where emotional blunting seems to appear more often in the long run with antidepressant treatment. In fact, the authors themselves state in their discussion that: “the OQuESA measures one or more aspects of depression, rather than necessarily measuring only emotional effects.”\textsuperscript{24} The authors state that appropriate double-blind studies are under way using the questionnaire, hopefully clar-
ifying the question of overlap between depressive and residual symptomatology. However, it would have also been interesting to look for correlations between the BDI and the OQuESA, which unfortunately has not been analyzed in this study.

Possible mechanisms of emotional blunting
In an excellent review of case reports, Barnhart et al discuss two mechanisms:
(i) Frontal lobe activity may be modulated through serotoninergic projections, finally leading to emotional blunting. 
(ii) SSRIs may influence serotoninergic systems, which in turn might modulate midbrain dopaminergic systems also projecting to the prefrontal cortex and triggering emotional blunting.

Clinical management of emotional blunting
According to Barnhart et al, there are three different ways to manage or respond to emotional blunting. Probably, the simplest approach is to reduce the dosage of the antidepressant. In most case reports, particularly in patients taking SSRIs with a shorter half-life, a dose reduction led to complete resolution of emotional blunting. However, in these cases, this effect typically occurred later, after several months of treatment with an antidepressant. Earlier, it might be even more difficult to distinguish emotional blunting from depressive symptomatology. Thus, one might not want to put the patient at risk of worsening depression through antidepressant dose reduction. A case report described the resolution of emotional blunting when bupropion was added. The addition of bupropion is also a well-established augmentation strategy.

This strategy might especially be helpful in patients with a partial response to an antidepressant and where it is not clear to what extent the phenomena might be attributable to the initial depressive episode. The third and last management option would be to switch the antidepressant. Based on the above observation that dose titration was a more effective strategy with short–half-life SSRIs, one might think of switching to an SSRI with a shorter half-life. Some case reports also described patients experiencing apathy with an SSRI and who did not experience apathy after switching to monoamine oxidase inhibitors or TCAs.

An interesting new alternative might be a switch to agomelatine. This is an antidepressant whose properties (MT₁/MT₂ agonist and serotonin 2C [5-HT₂C] antagonist, causing no release of serotonin in the brain) might protect from emotional blunting with a pharmacologic effect that is primarily upon circadian synchronization and enhancement of dopaminergic and adrenergic input to the frontal cortex through the synergy of its receptors. Agomelatine facilitates positive versus negative affective processing, including emotional memory and fear-potentiated startle.

Conclusion
There is a wide range of evidence available suggesting that the psychological antidepressant effect of pharmacologic treatments can arise from a reduction in negative bias in emotional processing. Apart from positive effects, emotional blunting has been discussed as an unwanted emotional side effect. There are specific rating instruments available and several reports suggest the existence of emotional blunting under SSRI treatment. However, so far there are no convincing criteria that can separate emotional blunting from residual depressive symptoms. Clinical reports suggest that emotional blunting tends to appear rather late with SSRI treatment and also seems to be dose dependent. Thus, a dose reduction or switch to an SSRI with a shorter half-life might be the first choice in the management of emotional blunting.

References


**Keywords:** agomelatine; antidepressants; emotional blunting; iatrogenic effect; SSRI; tricyclic antidepressants
THE QUESTION

When treating depressed patients, physicians usually first consider negative emotions. But isn’t that only one side of the story? It is increasingly appreciated that there is more to the management of depression than the war against the darker side of things. Contributors to this section draw on their experience to discuss the rationale for simultaneously taking positive and negative emotions into account and the potential implications this has for the patients.

Do you take positive emotions into account while treating depressive patients?

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Emotional disorders are paid less attention in psychiatry than affective disorders. It is not a coincidence, as discrete emotional reactions to specific events are rare causes for medical consultation, and usually reflect an underlying mood alteration such as depression. For depressive patients, the issue is not so much the loss of their usual and almost imperceptibly “normal” mood, but rather an emotional reaction that develops in acute form (e.g., anguish, sadness, anger), instantly uniting all body functions. The essence of the psychic mechanisms that develop and intensify these emotions lies not in their potentiation by depressive affect, but in their compensatory role: the emotions compensate, at least in part, for lowered mood, and are thus necessary to maintain life activity. Consideration of emotional reactions plays an important role when choosing a treatment strategy and individualizing therapy, and also in ensuring treatment compliance and predicting antidepressant effectiveness.

The decisive role of emotions in governing human actions is reflected in the motivation theory of emotional origin, which postulates that emotions and motivations are essentially similar. The question of which emotions to consider in ensuring compliance and motivation of a patient is not rhetorical. In positive psychotherapy, positive emotions are developed, whereas psychoanalysis focuses on eliminating negative emotions.

The issue is tied to numerous psychological theories on the origin and role of emotions in human life. A black-and-white division into positive and negative emotional states is an oversimplification of complex events: negative emotions may give rise to a positive emotion (e.g., envy of a person changes into joy after that person’s defeat) and emotions may be positive and negative in different moments (e.g., melancholy caused by romantic love). It is not emotions themselves, rather their effects on human activity and the impression they make on others that is positive or negative. Therefore, negative emotions are as necessary and adaptive as positive ones. Doctors should consider the entire emotional spectrum in depressive patients to attain compliance. The more a patient shows both positive and negative emotions (especially during first treatment steps), the more successful is the process of motivation. To a great extent, this depends on the doctor’s competence in helping patients become aware of their own emotions and to value them (reflective training); not trying to replace the negative emotional background with an artificial positive one. When the quality and amount of information given is inadequate (including about planned treatment), emotions also fill in for lacking information, compensating for unavailable knowledge (cognitive component of emotions). Thus, the process of informing a patient is an additional part of emotion management in depression.

Emotions are closely connected to neurophysiological systems, and there is a relative interaction with cognition and dependence on needs. Notions of negative and positive emotions are also relative. This ambivalence is especially obvious for the emotion of expectation (anticipation): it combines the wish for something to happen (positive component) with concern that this might not happen (negative component). Expectation performs a prognostic function and manifests as stress augmented by uncertainty. This emotion (expectation, feeling of future treatment success or failure) is considered a trigger to the placebo effect. We developed the Questionnaire of Therapy Expectations (14 items) to obtain information about depressive patients’ expectations of pharmacological treatment. Several topics were surveyed: whether patients consider their condition to be (un)treatable, previous experiences with depression treatment (positive or negative), expected time frame for onset of therapeutic effect, and whether treatment side effects are expected and, if so, how severe. After a week of placebo therapy, most responders were found to have positive expectations (39.7%) and only 3.6% had been unsure. Placebo nonresponders included all patients with negative expectations (34.9%) and 21.6% of unsure patients. As the placebo effect is an important part of antidepressant activity, the emotion of expectation may predict whether or not pharmacological treatment will be effective.

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Emotion is the generic term for subjective, conscious experience characterized primarily by psychophysiological expressions, biological reactions, and mental states. The most distinct classification of emotions to date is probably Parrot’s 2001 theory. Parrot identified over 100 emotions and conceptualized them in a tree-structured list comprising primary (fear, anger, sadness, surprise, joy, and love), secondary, and tertiary emotions. Emotions can also be grouped on a positive or negative basis; e.g., joy versus sadness, trust versus distrust, or surprise versus anticipation.

Many different components of emotion form integral parts of the clinical syndrome of depression, but a mood disturbance is considered the core symptom in depressive disorders. However, depressed mood and negative emotions like sadness do not necessarily constitute a psychiatric disorder. They are a normal reaction to certain life events, symptoms of some medical conditions, and a side effect of some medical treatments.

Although the subjective feelings described and expressed by most melancholic people do bear some resemblance to the mood changes of everyday life, they clearly go beyond the common experience. A patient suffering from depression experiences painful negative emotions, and has an inability to respond to or generate pleasurable stimuli. The painful dimension of depressive experience during illness is usually related to anxiety, guilt, anguish, and restlessness—an agitated state of emotional arousal that we consider to comprise negative emotions. A general blunting of emotions is considered an important feature of clinical depression. Positive emotions such as enjoyment, happiness, passion, enthusiasm, and excitement are typically reduced in people suffering from depression. Most importantly, negative emotions like sadness, anger, aggression, and anxiety are usually increased in depressive states. Interestingly, the term emotion does not appear in the symptom description of major depression in both the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Statistical Classification of Diseases, Tenth Revision (ICD-10) classification systems of mental illness.

Some patients suffering depression report subjective negative emotional symptoms that seem to arise as an adverse effect of antidepressants and lithium salts. This phenomenon was described in the early 1990s as emotional blunting; for example, in patients treated with selective serotonin reuptake inhibitors (SSRIs). Dose-related symptoms that disappeared shortly after withdrawal of fluvoxamine or fluoxetine were apathy, indifference, loss of initiative, and disinhibition. Overall, relatively little research has been published to clarify whether symptoms of emotional blunting are indeed related to treatment with SSRIs or represent residual symptoms of depression. Recently, a rating instrument, the Oxford Questionnaire on the Emotional Side-Effects of Antidepressants has been developed and validated. This scale offers the opportunity to measure emotional blunting during treatment with antidepressants in the clinical setting.

Depressed people may experience a variety of different positive and negative emotions, the latter including sadness, anxiety, emptiness, hopelessness, worry, helplessness, worthlessness, guilt, irritability, hurt, or restlessness. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating and in remembering details or making decisions, and may contemplate or attempt suicide. These symptoms can come and go within hours, days, or weeks, and may give the patient the feeling of riding a frightening rollercoaster of emotions.

When positive emotions slowly return in a patient suffering from melancholic depression, it is often a first sign of response to treatment. Therefore, it is important to monitor not only the reduction in negative emotions, but also the return of positive emotions during treatment. It is also of clinical relevance to identify symptoms of emotional blunting that may occur during a course of treatment with psychotropic medications. This latter area of research has been widely neglected in the past.

References
Mood is an emotional state, although the terms mood and emotion may be used interchangeably. Moods differ from emotions in that they are less specific, less intense, and less likely to be triggered by a particular stimulus or event. Moods generally have either a positive or negative valence.

Clinicians usually manage to alleviate depressive symptoms, and most of the time they will be satisfied that they have regained the patient’s baseline (euthymic) mood. Patients will be pleased to regain their energy and restart functioning, but they will not necessarily feel or think positively about themselves, particularly if only treated with antidepressants. Studies indicate that the majority are apprehensive and worried that they may go back to their horrible gloomy mood, and usually fail to resist the recurrent negative themes during their recovery course.

Even though research on emotions has flourished in recent years, investigations that expressly target positive emotions remain few and far between. Any review of the psychological literature on emotions will show that psychologists have typically favored negative emotions in theory building and hypothesis testing. In doing so, psychologists have inadvertently marginalized the emotions such as joy, interest, contentment, and love that share a pleasant subjective feeling.

In contrast with biological treatment of depression, most if not all psychotherapy treatment models aim to alter the content of underlying cognitive structures that influence affective state and behavioral patterns. For example, in the case of apathy, resulting from a person’s expectation of failure in all areas, the patient is actively taught to experience reactive emotions through correction of their cognitive state.

In my clinical practice, I work with patients presenting with depression to try and understand its correlation with their adaptive abilities during stressful and difficult times, and I may use their intellectual belief, e.g., belief in God’s will, which is culturally accepted, to relieve their guilt and decrease sense of self-blame. In doing so, most of them will gradually experience joy, which will eventually help to improve their cognitive state. Additionally, I work with them on improving their social skills as an alternative means of reducing subsequent negative impacts resulting from and/or causing their depression, whether related to study, work, or even relationships.

Studies have reported impaired executive function in patients with major depressive disorder, with positive correlations with depression severity and illness duration. There are also studies suggesting that these patients have the same level of impairment, or less impairment, as depressed bipolar patients.

Happy people are more likely to succeed in achieving culturally valued goals (e.g., work, love, and health) than their less happy peers. However, the large number of available correlational studies in this area includes research examining behavior and cognition in parallel with successful life outcomes—that is, the characteristics, resources, and skills that help people to succeed (attributes such as self-efficacy, creativity, sociability, altruism, immunity, and coping).

Despite the increased focus on self-esteem over the past three decades, depression in children has continued to grow, now affecting a quarter of all children today. Although the midterm outcome is often favorable, the prognosis of depression in the young is often poor, with 75% experiencing relapse at 5 years, thus considerably increasing the risk of depression in adulthood. To combat this trend, Dr Seligman began the Penn Depression Prevention Project, the first long-term study aimed at 8- to 12-year-olds. His findings were revolutionary, proving that children can be protected against depression by being taught how to challenge their pessimistic thoughts (Seligman’s learned optimism).

References
At first glance, the question seems to be nontraditional and unusual, especially for psychiatrists with a strict psychopathological, Kraepelinian, and “antipsychodynamic” orientation, which is common in the post-Soviet countries. This approach is considered to help avoid missing the transition to hypomania, and differentiates unipolar depression from bipolar II and mixed states.

However, the meaning of the question, and hence the role of positive emotions in the treatment process, appears much more profound when one considers the dramatic impact that psychodynamic and interpersonal factors have on responsiveness to pharmacological treatment for depression—i.e., transference and countertransference, defense, conscious and unconscious benefits derived from the state of depression, etc. An important part of the treatment process also involves knowledge of a patient’s previous life experience—i.e., their behavior and interactions when in a good mood state with positive emotions.

Practical experience suggests that psychological and psychodynamic factors such as the image of psychiatrists, the style of doctor-patient communication, therapeutic alliance and positive transference, patient expectations and readiness to change, and secondary gain could be even more potent in determining treatment outcome than the biological effects of antidepressants. It seems to be very important during the treatment process to demonstrate and remind patients of their life—including emotions, attitudes, activities, and interactions—before and outside of the period of depression. In other words, not to tell them what is bad when in low spirits, but why it is good to be cheerful and positive and what secondary gains could be reached in different areas of their life from a good mood state with positive emotions. In doing so, it is necessary to emphasize that depression is not “an eternal punishment,” but a time-limited state of illness that, without fail, will eventually give way to a state of health and good mood. This gives an opportunity to make a patient “ready to change,” and in many cases, his motivation to be healthy and cheerful is the most powerful determinant of treatment effectiveness—sometimes more powerful than the type of antidepressant and its dosing, etc. When communicating with patients, it is vital to convey that drug treatment is not a mechanical process of taking pills, but the route away from sadness and suffering to a healthy emotional state and a good, valuable life.

One of the most potent ingredients in antidepressant treatment is the positive transference to the doctor, as well as his or her capacity to stimulate the patient’s positive emotions and expectations. At this point, it is of value to emphasize the importance of proper communication skills and a nondepressive manner; to be able to emit confidence, calmness, endurance, and professional competence. The doctor’s ability to be positive, emotionally stable, cheerful, and tolerant promotes positive transference and hence a therapeutic alliance, adherence, and higher placebo response, with a positive therapeutic outcome as a result. By contrast, pessimism on the part of the doctor and a lack of the aforementioned qualities is associated with negative transference and hence nonadherence, distorted communication, and a paradoxical situation in which medications serve to be countertherapeutic or the aims of the patient become defensive.

References
When prescribing antidepressants, one should closely monitor changes in background emotional state in addition to core therapeutic response. Negative emotions naturally command the patient’s attention, but subtle (“extratherapeutic”) positive changes in emotional response to daily events also occur and may deserve recognition, as they inform about the biology of emotional regulation. Besides these often-neglected aspects of antidepressant action, I invite your attention to a particularly distressing emotion formerly known in English psychiatry as “precordial anguish,” and as “angoisse” in French and “angustia” in various Latin languages, a symptom that has all but disappeared from contemporary psychopathology.

Subtle positive changes in the emotional state of some patients in response to treatment were described early in the literature, chiefly with monoamine oxidase inhibitors, but they only received special attention in the 1990s after the introduction of single small doses of selective serotonin reuptake inhibitors. Before that, they could hardly be noted due to sedative or anticholinergic effects, or “blunting” of emotions, induced by various medications.

To determine whether such positive effects are extratherapeutic, my colleagues and I conducted a series of experiments in volunteers without personal or family history of psychiatric disorders. For the active drug we chose clomipramine, since it induced such changes with small doses in our patients with panic/agoraphobia. In double-blind experiments with propantheline as active placebo, we measured variables of personality, mood, cognition, performance, sleep, and neuroimaging. We identified four domains of subjective change: interpersonal tolerance (decreased irritability and tension in social interactions), efficiency (improved decision-making, ability to prioritize demands, and self-confidence), well-being (feeling better, brighter mood), and feeling substantially changed from usual self. About 35% of participants met the response criteria for such changes. Selecting the responders, we carried out a final crossover trial of three weeks on active drug or placebo.

All participants maintained (or reacquired) the response criteria on clomipramine, and lost it on placebo. We concluded that low doses of clomipramine may induce positive changes in emotional response in the absence of psychopathology in some, but not all, individuals. We are now submitting the neuroimaging findings of this trial for publication, which show significant differences between responders and nonresponders (Cerqueira et al, in preparation).

I also pay attention to negative emotional changes in my patients, and I try alternative medications to avoid them.

Turning to the concept of “anguish,” the feeling of precordial oppression was described in psychiatric texts in most Latin languages, as well as in English (“precordial anguish”) and German (“Oppressionsgefühl”) texts. Specific words for this ancient emotion are available in unrelated languages, such as Chinese, Hungarian, and Arabic, suggesting a consistent experience across time and cultures. Its distinction from anxiety was lost by modern psychopathology in the 1960s due to problems of translation for “angst,” and because there was no compelling reason to discriminate it from anxiety before modern psychiatric treatment.

Anguish combines the ideas of present pain and agony of mind, and is not universally experienced. It occurs in about one-third of my patients with depressive disorders, typically in melancholic or bipolar depressive states with early morning awakening, but also in the evening in those with inverted diurnal variation, as well as patients with schizoaffective disorders. They clearly distinguish precordial anguish from anxiety, but it may be confused with precordial pain during a panic attack. Anguish is also described, in low intensity, by normal adults and children. Its residual presence at an improving stage means that dysfunction is still present. The pathophysiology of a symptom localized in the chest may primarily involve somesthetic systems related to visceral organs. A drug capable of promoting remission of depressive syndromes must suppress this symptom. The mechanisms, however, require scientific investigation.

References
Emotions can be defined as multicomponent responses that develop in a relatively short space of time in response to internal or external stimuli that include subjective experiences, cognitive processes, and psychophysiological changes. Experiencing positive and negative emotions is unavoidable, and at times useful, and both have been selected along the human evolutionary path for their adaptive and survival value. However, negative emotions, when long lasting, deep, or inappropriate, can trigger anxiety disorder or depression and can impair the immune system. Perhaps this is the reason that although research on emotions has increased continuously in recent decades, the majority of studies has focused on negative emotions rather than positive emotions, such as joy, interest, contentment, and love, which all share a pleasant subjective feeling. Experiences of positive emotion are central to human nature and contribute richly to the quality of people’s lives, and they have only recently begun to attract research attention, mainly for their impact on psychiatric disorders, especially depression.

In fact, according to some theorists, depression is a disorder in which the core symptoms are represented by a deficit of positive affect and inability to experience positive emotions. This notion is supported by different functional magnetic resonance imaging studies showing that the brains of depressed patients exhibit an overall decrease in activity in the regions of the brain responsible for generating pleasure/reward/positive emotions. Furthermore, other scientists report that although the initial levels of activity in positive/pleasure-generating brain regions are no different between depressed patients and healthy control subjects, patients do not seem to be able to sustain positive emotions. In terms of treatment strategies for depressed patients, in order to take advantage of these emerging findings, more sophisticated and integrated strategies will be needed that are not limited to prescription of drugs, but also include behavioral and cognitive therapies, as well as triggering of coping styles marked by finding positive meaning. With regards to behavioral interventions, patients should be assisted in clarifying their medium- to long-term goals, and in engaging more in pleasant activities. However, psychological treatment should also focus on helping patients to develop a more distributed happiness. Depressed individuals (and non-depressed individuals, for that matter) should create a life in which they receive pleasure and reward from multiple areas of their existence. This bottom-up (behavior to brain influence) approach is more likely to lead to long-term, enduring, positive emotions.

This approach can be achieved by placing more emphasis on finding positive meaning, which seems to be fundamental to eliciting positive emotions. It is noteworthy that positive emotions may not need to be intense or prolonged in order to produce a beneficial effect. Positive emotions can broaden the individual’s thought-action repertoire, which builds and promotes their personal resources. This psychological process can increase an individual’s receptiveness to further pleasant or significant events, while also increasing the odds of finding positive meaning in those events and experiencing further positive emotions. This can in turn trigger an “upward spiral” that might, over time, improve depressive symptoms. Thus, the experience of positive emotions might facilitate coping and alleviate depressed mood.

In conclusion, different lines of recent studies support the notion that depression is best treated by an integrated psychological approach aimed at promoting positive emotions in combination with prescription of drugs, and not use of drugs alone. Future antidepressants should be targeted specifically at restoring or improving a patient’s ability to experience positive emotions.

References
Do you take positive emotions into account while treating depressive patients?

I do take into account positive emotions in the treatment of depressive patients, by considering their stimulation through neurofeedback. In fact, in many depressive patients, stimulation of positive emotions can be an effective adjunct to pharmacological treatment. Why? A robust body of research has documented that depression is associated with differential activation of the right and left prefrontal cortex. When there is a biological predisposition to depression, frontal asymmetry can be observed with more left frontal alpha activity, meaning that the left frontal area is less activated. Electroencephalogram (EEG) studies have demonstrated that the left frontal area is associated with more positive affect and memories, and the right hemisphere is more involved in negative emotion. Thus, when the left hemisphere is basically stuck in an idling alpha rhythm, there is more withdrawal behavior, in addition to the deficit in positive affect. This means that depressed patients may be anticipated to be less aware of positive emotions, while at the same time being more in touch with the negative emotions that are associated with the right hemisphere.

In addition, evidence also suggests that positive emotions are important facilitators of adaptive coping and adjustment to acute and chronic stress, mainly by sustaining coping efforts, providing a breather, and restoring depleted resources.

It has been proposed that this frontal asymmetry (alpha asymmetry) may represent a state marker of depression, although such an asymmetry is not necessary or sufficient for the production of a specific type of affective style or psychopathology. Differences in prefrontal asymmetry may be most appropriately viewed as diatheses that bias a person's affective style, and thus in turn modulate a person's vulnerability to develop depression. It has also been found that alpha asymmetry can be used to predict the response to antidepressants before the beginning of pharmacological treatment, in such a sense that it could serve as an aid in the choice of treatment.

As we gain insight into the relationship between depression and EEG patterns, and in view of the fact that EEG biofeedback (neurofeedback) has been found to be effective in modifying brain function, producing significant improvements in several clinical symptoms, use of neurofeedback in depression is being proposed as a way of training depressed people to change their frontal alpha asymmetry so that it resembles the asymmetry pattern found in nondepressed individuals. As with any form of biofeedback, neurofeedback is built upon the self-learned practice of conscious generation of more healthy organic patterns. The technique represents a form of operant conditioning through which an individual may learn to modify the electrical activity of his own brain. Some patients claimed after training that they could distinguish between emotions generated by depression and those associated with life situations.

Taking into consideration all of the aforementioned information, when planning a therapeutic strategy for depressive patients, I also consider adjuvant neurofeedback training in addition to pharmacological treatment to facilitate patient learning of how to modify their frontal activity by increasing activation of the left hemisphere and decreasing activation of the right hemisphere.

To sum up, asymmetry training is important for controlling and regulating emotion, and it may facilitate left frontal lobe function in depressive patients.
As trainees and young psychiatrists, we are taught about psychopathology. We learn to diagnose psychiatric disorders based on abnormal signs and symptoms related to this psychopathology. Treatment, then, aims to eliminate these signs and symptoms. In depression, as defined by criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (Text Revision; DSM-IV-TR), the main therapeutic objective is remission: to improve mood, apathy, guilt, and hopelessness, as well as sleep and appetite—in short, the clinical signs of the disorder. The majority of these symptoms will improve with current treatments. However, a significant number of patients experience only partial remission. Although they do not have sufficient symptoms in number or severity to constitute a disorder, they do still have some symptoms and they feel that they do not have the same emotional well-being as before. For many, even though they no longer feel depressed, the anhedonia is still present. The presence of such residual symptoms is associated with a higher relapse rate, socioeconomic impairment, and increased utilization of health care services. Positive emotions such as love, joy, hope, and passion do not return; the joie de vivre remains elusive. Increasingly, there is evidence that positive and negative emotions play a part in the treatment of and recovery from depression. There is a close relationship between depression and physical illnesses such as myocardial infarction, stroke, and cancer. Patients suffering from a physical illness with concomitant depression have a poorer outcome compared with patients not suffering from depression. Patients with an existing negative emotion profile (introversion, low sensation seeking, autonomy, dysfunctional attitudes, high displeasure capacity, passivity, and pessimism) are at higher risk of developing depression. Positive emotions have been shown to be protective in the prevention of stress and depression. They build resilience. Numerous studies show that happy individuals are successful across multiple life domains, including marriage, friendship, income, work performance, and health. Furthermore, the evidence suggests that positive affect—the hallmark of well-being—may be the cause of many of the desirable characteristics, resources, and successes correlated with happiness. A twin study looking at positive emotions found that such emotions buffer against the genetic risks of developing depression. Indeed, having positive emotions has been associated with a longer lifespan. In a study of Catholic nuns, positive emotional content in early-life autobiographies was strongly associated with longevity six decades later.

In light of such evidence, recognizing and optimizing the presence of such emotions early in the treatment of depression would lead to better outcomes. A recent study suggests that looking beyond the elimination of the abnormal signs and symptoms of depression, the early improvement of positive emotions predicts remission from depression after pharmacotherapy. Apart from our established treatments for depression that are aimed at achieving an absence of symptoms, we should keep in mind the use of neurobiological treatments, psychosocial therapies, and the spiritual needs of patients to help patients better cope with stress and optimize positive emotions. Having the return of positive emotions as a treatment goal would lead to a better quality of life and lessen the risk of relapse for individuals suffering from depression. To ignore this would be a disservice to our patients as well as to ourselves.

References
Despite the importance of negative emotions as major criteria in the diagnosis of major depression, positive emotions are unfortunately frequently not taken into account when treating depressive patients.

Anhedonia, a negative emotion, is considered a core symptom of major depression that involves deficits in the ability to experience positive emotions such as pleasure, pride, happiness, and amusement. 1 Depressed patients thus suffer from decreased hedonic ability, which is defined as the amount of positive affect that it is possible for an individual to experience over time. 2 Moreover, anhedonia may not entirely be due to a tonic decrease in the ability to experience pleasure, but rather an inability to preserve positive impact and honor responsiveness.

The value of positive emotions lies in their capacity to enable individuals to build durable personal resources (ie, intellectual, physical, psychological, and social). In addition, positive emotions affect people’s thinking style, social interactions, and physiological responses. 3 Positive emotions also broaden the breadth of people’s thinking, attention, and actions moment to moment, while negative emotions narrow it. Thus positive emotions are considered as efficient antidotes to the lingering after-effects of negative emotions. 4 However, the ultimate goal in managing depressed patients is to understand how positive emotions might accumulate and compound each other to transform the lives of patients for the better. Hence, there can be several reasons for taking positive emotions into account when treating depressive patients.

First, the proper deconstruction of the depressive episode into all its component positive and negative emotions through the use of self-reports or assessment scales is crucial in detecting a patient’s positive resources, recognizing their character strengths, and helping the patient respond actively and constructively to positive events reported by others.

A second reason is to discuss optimism and positivity using an explanatory style: optimism is to see bad events as transient, changeable. The retrieval of positive and negative memories in relation to current events and their role in the subsequent development of positive and negative emotions is also noteworthy. 5

A third reason for taking positive emotions into account is the conceptualization of depression as involving low self-esteem, whereby self-relevant stimuli trigger negative self-appraisals that may dampen the individual’s ability to experience positive self-relevant emotions such as pride, possibly due to a dysfunctional emotion system. Indeed, the need to delineate the relationship between negative self-appraisals and self-relevant positive emotions is crucial when treating depressed patients. Furthermore, it is important to bear in mind that positive self-relevant emotions are multifaceted and include positive emotions associated with personal achievement as well as those based on group membership. 6

In conclusion, in psychiatric clinical practice, therapists should consider taking into account negative and positive emotions simultaneously during the management of depressed patients. With regard to positive emotions, therapeutic approaches should not only encourage patients to participate in potentially enjoyable situations, but to practice allowing their pleasant emotions to surface instead of suppressing them.

References
The simple answer to this question is “yes, of course.” However, there are other questions involving “why, when, and how” that can explain the rationale behind this simple answer.

Why: it is interesting that even the scientific literature on emotions includes far more publications on negative emotions like fear, anger, and sadness than on positive emotions like joy, interest, and contentment. In 1998, Fredrickson proposed that positive emotions broaden a person’s momentary thought-action repertoire. Thus, according to this view, positive emotions and related positive states are not only linked to broadened scopes of attention, cognition, and action, but also to enhanced physical, intellectual, and social resources. As emotional intensity has been found to be one of the strongest predictors of outcome in depression, positive emotions may play an important role regarding the values and objectives of patients. Depressive patients frequently want to decrease their experience of negative emotions and increase their experience of positive ones.

When: it has been hypothesized that a patient’s response to their depressive symptoms plays a role in either amplifying and perpetuating or alleviating their depression. In 1995, Morrow and Nolen-Hoeksema put forward the idea that emotion-focused coping would be expected to perpetuate depression symptoms, whereas task-focused coping or social distraction might be expected to help alleviate depression. In a study evaluating the impact of a range of psychosocial factors on the outcome of major depression, it was found that interpersonal events and responses to depression (ie, coping) play an important role. This means that positive emotions should be taken into account at every stage in the management of depression, from diagnosis to treatment.

How: antidepressants do not act as direct mood enhancers, but rather change the relative balance of positive to negative emotional processing, providing a platform for subsequent cognitive and psychological reconsolidation. While similar in efficacy to other antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are generally considered to be better tolerated, and thus have a high market share as a consequence. However, an unforeseen and common side effect of these drugs can be emotional blunting, which is really underestimated. Although blunting of emotion is not described as a potential side effect in package inserts, many clinicians have noted that patients being treated with SSRIs frequently complain of this.

In a study conducted in 2002 by Opbroek and colleagues, compared with controls, depressed patients reported significantly less irritation, ability to cry, ability to care about other’s feelings, sadness, erotic dreaming, creativity, surprise, anger, expression of their feelings, worry over things or situations, sexual pleasure, and interest in sex. A qualitative study in 2009 by Price et al also revealed that almost all depressed participants in the study described a reduction in their positive emotions, which they attributed to their drugs. Participants reported a reduction in a wide range of positive emotions, including happiness, enjoyment, excitement, anticipation, passion, love, affection, and enthusiasm. Yet, this may not be the only destiny for depressed patients; agomelatine, a new drug with a novel pharmacological action, was studied for its effects on emotional processing in healthy volunteers and was found to decrease subjective ratings of sadness, reduce recognition of sad facial expressions, and improve positive affective memory. Clinicians should therefore routinely ask patients about emotional side effects when they are assessing progress on antidepressants, and positive and negative emotions should simultaneously be taken into account in the early phases of treatment.

References
Major depressive disorder (MDD) is a heterogeneous condition with complex neurobiological correlates that are still not fully understood, and it is one of the most prevalent mental illnesses. Current drug therapy is suboptimal. Response rates to a single antidepressant are generally considered to be 60%-70%, with over 80% of the drug effect accounted for by placebo effects. Remission appears in only 30%-40% of the depressed population. Unfortunately, about one-third of patients will not remit even after two to four pharmacotherapy trials. Vulnerability to relapse persists after remission, and this has been attributed to abnormal biases in the processing of emotional stimuli in limbic circuits.

Leaving aside the limited efficiency of antidepressants, evidence suggests that about 60% of improvement with an active antidepressant takes place during the first 2 weeks of treatment. Several meta-analyses have shown that early improvement after 1 or 2 weeks of treatment strongly predicts later treatment outcome. Better knowledge of the mechanisms involved in early treatment response may help us to optimize clinical decision-making and improve quality of life in our depressive patients. MDD is characterized by impaired cognitive and emotional processing, which is why modulation of emotional processing is an intended outcome of both pharmacological and psychological treatment.

Although studies show that antidepressants affect processing of both positive and negative emotions, recent studies suggest that changes in positive rather than negative emotions may be important in predicting recovery from depression. Patients with MDD usually report increased suppression of both negative and positive emotions.

Currently, recovery from a depressive episode is still measured by reduction of unpleasant symptoms and not restoration of a normal range of emotional experience. Drugs or psychotherapies actively targeting the positive affect (PA) or reward system may be more efficient in triggering recovery processes. Functional imaging suggests that anticipatory reward may localize to dopaminergic areas in the nucleus accumbens, ventral tegmental area, orbitofrontal cerebral cortex, and medial prefrontal cortex. Patients who have anhedonia are impaired in their ability to sustain upregulation of PA, and this is associated with reduced frontostriatal connectivity.

There has been an increase in the number of studies on positive emotions during the last few years. PA and negative affect (NA) have been defined as “subjective moods and feelings,” where PA represents pleasant engagement in positive feelings (eg, excitement, interest) and NA reflects distress and unpleasant reactions to the environment (eg, fear, shame).

PA and NA have only recently become a focus of pharmacological research. Harmer and colleagues were the first to suggest that serotonergic antidepressants may “constrain” emotional responses across both NA and PA. They showed that selective serotonin reuptake inhibitors (SSRIs) diminish the neural processing of both rewarding and aversive stimuli, and helped to explain the often reported emotional flattening effect of SSRIs.

The ability to generate PA boosts (reward experience) from pleasant daily life events preserves mental health. Positive emotions also predict psychological resilience. Novel treatments that facilitate positive affective processing are required, and in this context, agomelatine has emerged as a promising option. Agomelatine is a new antidepressant with synergistic melatonergic agonism and 5-HT2c antagonism. This interaction underlies its efficacy in restoring circadian rhythms and mood; response rates of about 80% have been consistently reported across several trials. Furthermore, agomelatine increases dopamine and norepinephrine release in the limbic system, which would explain its perceived benefits for PA. Findings from the Harmer study in healthy volunteers demonstrated early effects of agomelatine on emotional processing, reduced subjective reports of sadness, improved positive affective memory, and modulation of emotion-potentiated startle response. Finally, agomelatine has additional advantages over other available antidepressants, and has exhibited improvements within a week of administration, in particular in mood, daytime functioning, and importantly, anhedonia.

References
From a psychotherapeutic perspective, the question should not be if, but rather when and how we take positive emotions into account while treating depressive patients. Just as health is more than the absence of disease, positive emotions are more than the absence of negative emotions. Although negative emotions are the main focus of research on depression, clinical practice shows that positive emotions should and can be specifically targeted with psychotherapeutic treatments. There are at least four good reasons as to why this is important: (i) reducing negative emotions does not automatically improve positive emotions; (ii) positive emotions can reduce negative emotions; (iii) positive emotions help resolve problems that play a role in the etiology and maintenance of depression; and (iv) positive emotions may protect against relapse and recurrence by improving quality of life and well-being. Furthermore, there is preliminary evidence that depressive symptoms are associated with difficulties in adaptively regulating positive emotions.1

However, interventions for enhancing positive emotions are not a panacea for the treatment of depression. The “when and how” is crucial for their success or failure. An attempt to simply encourage a depressed patient to “feel positive” will most likely have no effect or even worsen the symptomatology. The reasons are obvious: emotions cannot be invoked directly, and depressed patients in particular may interpret the failure of such an “intervention” as their own fault. Thus, we need therapeutic interventions that indirectly induce positive emotions and are integrated into a comprehensive treatment plan that includes interventions for both positive and negative emotions, as well as additional therapeutic aims selected on the basis of the patient’s specific needs. For example, in the acute phase of major depression, symptom-oriented interventions may be the best strategy. But for residual depressive symptoms, interventions focused on positive emotions and psychological well-being may yield the most beneficial effects, especially because the absence of psychological well-being seems to increase the risk of a relapse into depression.2

Best results may be achieved with a sequential combination of symptom- and well-being-oriented psychotherapeutic strategies. This may also be a promising option for anxiety disorders: while considerable alleviation of symptoms was achieved in a study of cognitive behavioral therapy for panic disorder, the vitality dimension of quality of life remained largely unchanged over time.6 Since deficiencies in energy and “pep” may create a vulnerability to future adverse events, additional interventions aimed at enhancing well-being may help to achieve more complete and long-lasting beneficial effects.

In conclusion, although the reduction of negative emotions is one important aim in the treatment of depression, positive emotions play a significant role as well. Targeting positive emotions may improve treatment of depression. In recent years, a growing number of psychotherapeutic interventions aimed at enhancing positive emotions have been developed.

However, both clinicians and researchers should pay attention to “when and how” interventions for positive emotions should be integrated into a comprehensive treatment plan for depression.

References
Clinicians are trained to explore for positive emotions in depressive presentations, but only to the extent of screening for bipolarity. How many clinicians focus on positive emotions as part of their core management of unipolar major depression itself? Depressingly, I suspect only a minority do. I take positive emotions into account while treating depressive patients, not just as a nicety, but as a core element of both patient care and safety. Moreover, patients themselves rate the presence of “positive mental health” (eg, optimism, vigor, self-confidence) as the most important factor for them personally in determining remission from major depression.

Traditional medical models have focused on distress, dysfunction, and mortality. This is understandable given that such concerns drive patients to seek help, but it is a model under change as societal expectations of physicians change. Additionally, the clinician’s relationship to society has changed, with fear of litigation sometimes shaping the focus more toward hazards than hopes.

Loss of enjoyment and disengagement from activities (social, recreational, and occupational) are cardinal problems impacting sufferers of depression, anhedonia being a core symptom in definitions of major depression. Depressed patients seem to have selective attention for “negative” emotions (sadness, fear, irritability, inadequacy), potentially perpetuating their dysphoria, apprehension, and disengagement. It is important to note that for some patients, such emotions are part of a grief adjustment process rather than a pathological state. Where there is a major depression-related selective attention for negative emotions, it is important not to inadvertently reinforce these cognitions by only questioning about such symptoms.

By the same token, one must not invalidate distress by excessively minimizing its importance during sessions with patients. A balance is needed—the “art” behind the science of clinical care.

Genuine ardent expression of intent to restore positive emotional capacity in patients can have profoundly beneficial therapeutic effects. Not only is engagement and treatment compliance fostered, but instilling hope may help reduce risk ideations. Once hedonic drive and energy begin to improve in severe depressive states, full recovery relies both on reengaging with and enjoying social, recreational, and occupational activities. Reinforcing these positive aspects of life may help prevent relapse during the maintenance phase of care.

Positive emotions should be included in the assessment and management of depressive presentations as part of diagnostic formulation, risk management, and treatment of patients to a full emotional and functional recovery. As society increasingly considers well-being to be the key health outcome, failure to take positive emotions into account while treating depressive patients is in some ways missing the boat with regard to what patients and the broader community want from physicians in the modern era. If you are not already doing so, I encourage you to take positive emotions into account while treating depressed patients.

References
When dealing with the depressed patient, one can consider two complementary layers of reality. First of all, there is the objective, biological dimension, which among other things, involves genetic and biochemical factors such as serotonin or melatonin transporter proteins. Secondly, there is the subjective, psychoaffective dimension conveyed by the patient’s story, which the psychiatrist will listen to and analyze. On the one hand, this story tells the tale of all the breakups, grief, conflicts, and violence that the patient has lived through and the resultant anxiety, guilt, and loss of self-esteem that these life experiences engender, and on the other hand it also reveals the patient’s personal resources and ability to bounce back. Besides use of mere words, the depressed patient also conveys his or her story through tone of voice and body language. Indeed, the patient’s emotions flow through the story told.

The patient’s thoughts, conveyed by the narrative, will not be meaningfully put to use during current and future therapeutic care unless the psychiatrist takes into account the emotions, both negative and positive, that are expressed through this discourse. It is with this approach that one can best appreciate the reality of the depressed patient’s psychological suffering. Indeed, with any depressed patient, it is essential to seek to understand how the depressive state functions within the patient’s unique life story. It is important to find words to express the silent suffering of depression, to give it meaning. None of this is possible if the emotional dimension is distanced from the therapeutic approach. This is why, in a considerable number of cases, the use of the classic selective serotonin reuptake inhibitor (SSRI) antidepressants acts as a barrier to the treatment of depression, due to the significant impact these drugs can have on emotional state. Depression is not an accident that has to be overcome at any price by drugs.

One of the goals of treatment is precisely to allow patients to reclaim their existence and win back their self-esteem, a process which SSRIs, with their numbing of emotions, can repress. These drugs tend to estrange patients from reality, making life easier to deal with because anxiety, feelings, and sexuality are dulled, except that the patients become mere onlookers of their own life and their emotions are not integrated into their personality. By restoring a relative feeling of well-being, these antidepressants may prevent patients from contemplating the reasons for their suffering and thereby cause them to neglect the grieving process that is necessary to overcome the depression. Furthermore, these attenuated emotions may, at the same time, be displaced by somatic complaints (heart disease, etc), or they may resurface in a way that is much more dangerous to the integrity of self, in the form of delirium.
The diagnostic criteria for major depressive disorder (MDD), dysthymic disorder, and bipolar I disorder in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are the same for children and adolescents as they are for adults, with some minor modifications. To make a diagnosis of a depressive disorder, the most defining symptom is depressed mood. DSM-IV describes this as depressed mood most of the day, nearly every day, indicated by subjective report or observation by others. The other defining symptom is anhedonia (loss of pleasure), which DSM-IV describes as markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day.

In my clinical practice, I emphasize the importance of these two points or symptoms in order to diagnose MDD. When the symptoms present as continuous low mood and anhedonia not affected by environmental factors, this indicates biological abnormalities rather than purely psychological effects. Depressed mood that is involuntary and independent of environmental change has been investigated in several studies. Functional neuroimaging studies have most commonly associated depressed mood and sadness with abnormal neuronal activity in the medial prefrontal cortex, including the anterior cingulate cortex and orbitofrontal cortex. These areas receive innervations from serotongenic, norepinephrinergic, and dopaminergic pathways. As such, low levels of norepinephrine, serotonin, and dopamine may be associated with low mood. Reduced dopaminergic activity has been linked to decreased incentive motivation, anhedonia, and loss of interest. Increased functional dopaminergic activity has been linked to positive affect.

In view of this, it is clinically important to view negative emotions, that is to say, low mood, anhedonia, and blunting of affect, as a diagnostic tool with which to make the correct diagnosis of biological depression, and to take into account the amount of positive emotion present during the first visit to establish the severity of MDD. The less positive emotion there is present, the more severe the MDD. Scales for measuring negative and positive emotions must be used so that an objective measurement is made and patients can see the lowering of negative emotions and the increase of positive emotions as they progress in their treatment. An example of such a scale would be the Snaith-Hamilton Pleasure Scale to measure anhedonia.

In conclusion, MDD, dysthymic disorder, and bipolar I depressive disorder are all biological disorders, and changes in positive and negative emotions in patients with any of these conditions are due to biological abnormalities. As such, in the treatment of these patients, initial assessments and measurements of negative and positive emotions will help to determine treatment efficacy and progress and assist in establishing better compliance. An even better prognosis can be anticipated for patients who are able to experience and monitor the change from high to low levels of negative emotions and from low to high levels of positive emotions.

References
Valdoxan’s unique profile of antidepressant efficacy at the core of depression

by C. Muñoz, France

This article will review the efficacy of Valdoxan (agomelatine) at the core of depression, in other words, on main symptoms such as depressed mood and anhedonia. Sad mood and anhedonia, together with anxiety, are regularly seen in depressed patients and are among the most distressing symptoms of the disorder. Valdoxan demonstrated efficacy in treatment of depressed mood and early anxiolytic efficacy even in the most anxious depressed patients, both in randomized and in observational postregistration trials. Two studies evaluating the effect on anhedonia through use of a scale specific for that symptom (the Snaith-Hamilton Pleasure Scale) showed earlier and better improvement with Valdoxan than with venlafaxine in the restoration of pleasure and interest. These effects on anhedonia were reported by doctors and patients in real-life situations and are all the more important given the scarcity of data in the literature on the effects of available antidepressants on this core symptom of depression. Taken together, Valdoxan’s effects at the core of depression lead to recovery of emotional integrity and of social and cognitive functioning in depressed patients, insuring better quality of life during and beyond depression.

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To be effective, an antidepressant needs to target its antidepressant activity at the two main core symptoms of depression: depressed mood and anhedonia. Whereas most drugs have been evaluated in treatment of sad mood, there is not much data to consult in the literature about alleviation of anhedonia with antidepressants. Targeting the abatement of these symptoms is a challenge for antidepressant treatment to achieve complete recovery. Anhedonia has been defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as the diminished interest or pleasure in response to stimuli that were previously perceived as a reward during the premorbid state; anhedonia results in poor outcome during major depression and is also found as a residual symptom. Its recognition and treatment are key to treatment, as it is at the core of depression. Apart from rodents, where anhedonia serves as an animal model of depression, most studies do not specifically look for this dimension. Some antidepressants have been studied for their effect on anhedonia, but no specific assessment tool or scale has been used. Among the antidepressants evaluated, moclobemide was found to be better than clomipramide for alleviation of anhedonia in depressed patients, but the evaluation was done using specific items of the Depressive Mood Scale
(Échelle d’Humeur Dépressive [EHD]). Sertraline was evaluated for its effect on anhedonia in an 8-week, open-label study conducted in 140 depressed patients receiving sertraline treatment, using clusters of symptoms defined in the Inventory for Depressive Symptomatology (IDS). A significant improvement in hedonic function was found, but this improvement appeared late, occurring after improvement of the anxiety and depression clusters. Again, no specific tool assessing anhedonia was used in this study. For both studies, the use of nonspecific assessments could have led to a lack of sensitivity and specificity in anhedonia recognition.

On the other hand, conventional antidepressants have a negative impact on emotion recognition and processing. Emotional dysregulation is frequently described during conventional antidepressant treatment, after depression remission, as residual symptoms. Furthermore, these effects can be distinguished from the depressive process, as confirmed in healthy subjects, such as in a recent study comparing citalopram and reboxetine, in which treatment with selective serotonin reuptake inhibitor (SSRI) reduced activation both in response to the reward stimuli and to the aversive ones. These results raise the possibility of antidepressant-induced emotional blunting. However, it is difficult to differentiate residual symptoms, revealing lack of efficacy of the treatment, from emotional side effect of the drug. Emotional blunting is experienced by patients as impairment in resolving their own emotional issues, modification of their personality, or insensitivity to their environment including peers, family, and routine tasks. These secondary effects have a direct impact on cognition and social functioning, and lead to pervasive impairment during maintenance treatment.

Valdoxan (agomelatine) has a novel and unique pharmacological profile in the antidepressant armamentarium. It is an agonist at MT1/MT2 receptors and an antagonist at 5-HT2C receptors. These receptors act synergistically to contribute to the efficacy of Valdoxan in depression. Valdoxan’s distinctive antidepressant properties have been evaluated and reported in clinical randomized trials versus placebo and available antidepressants and, since its marketing authorization in 2009, several observational studies have replicated and confirmed its antidepressant efficacy in daily clinical practice.

Because of its different pharmacological profile, also characterized by a lack of effect on serotonergic release in the brain, it was of interest to determine the effect of Valdoxan in the processing of emotional information which may be key for its distinctive efficacy on the core symptoms of depression. Indeed, a study with healthy volunteers demonstrated the early effects of Valdoxan on emotional processing, evidenced by the selective reduction in subjective reports of sadness, improvement in positive aspects of emotional memory, and modulation of the emotion-potentiation of startle response. These first results suggested that Valdoxan could have an impact on emotional processing in depression and anxiety and an earlier efficacy on positive affect in particular, therefore making the efficacy of Valdoxan different from conventional antidepressants.

This article will review the unique efficacy of Valdoxan on the core symptoms of depression that leads to improvement in emotional processing and functioning of depressed patients.

Valdoxan provides efficacy at the core of depression

The efficacy of Valdoxan in depression has been evaluated by the effects on all symptoms, with special attention to the key symptoms of depressed mood, anhedonia, and anxiety. Indeed, these symptoms are regularly seen in depressed patients and belong to the most distressing ones of the disorder.

Valdoxan is effective on depressed mood

The effect of Valdoxan on depressed mood has been evaluated in comparison with placebo treatment in an analysis of a pool of three placebo-controlled studies, and confirmed in two observational studies. The three placebo-controlled studies were multicenter, double-blind, randomized trials of Valdoxan for major depressive disorder (MDD) and the patient population was similar: outpatients fulfilling DSM-IV criteria for MDD, with a higher proportion of females than males (around 2/3) and a Hamilton Depression Rating Scale (HAMD) score at inclusion of 20-22.

After 6 to 8 weeks of treatment, Valdoxan was significantly better than placebo in the exploratory analysis of item 1, depressed mood, in the HAM-D scale, and this whatever the

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severity of depression at inclusion. The difference with placebo in favor of Valdoxan was significant not only for the total population, but also for severely depressed patients at inclusion (Figure 1). 17

The observational study VIVALDI (Valdoxan Improves depressive symptoms And normalizes ciriDaN rhythms) used the shortened version of the Montgomery-Asberg Depression Rating Scale (svMADRS) to evaluate the antidepressant efficacy of Valdoxan in 3317 depressed outpatients in Germany, of which 38.1% had neuropsychiatric comorbidities. The mean score of the svMADRS at inclusion was 30.6 (±8.7). The results showed a general decrease in the svMADRS total score to 24.2 (±9.7) already after 2 weeks of treatment and to 12.8 (±9.7) after 12 weeks. After the treatment period, the individual item representing depressed mood, “apparent sadness,” showed an improvement in 72.3% of the patients. 18

Another observational study, CHRONOS (not an acronym), was performed in the Russian Federation with a total of 6276 patients included in the study. The majority of patients (80%) were treated as outpatients and 20% as inpatients in psychiatric facilities. Considering all patients, most of them (82%) suffered from moderate (according to International Classification of Disease [ICD]-10 criteria) depressive episodes, either single (44%) or recurrent (38%). The mean 17-item HAM-D total score at baseline was 22.5±6.9. Valdoxan was usually given as monotherapy and comorbidities excluded psychotic symptoms. This study showed a rapid and significant (P<0.00001) improvement in the total HAM-D score, already present at week 1 (decrease to 19.5±7.1) and continuing onwards. The final score after the 8 weeks of treatment was of 4.7±4.7 (P<0.00001). The score for the depressed mood item of the HAM-D scale decreased in the patients treated with Valdoxan early in the treatment. 14

◆ Valdoxan demonstrated early and continuous restoration of pleasure and interest
Anhedonia has been evaluated in two specific studies, one versus baseline and the second versus venlafaxine. 21,22 These studies used a specific and validated anhedonia scale, the Snaith-Hamilton Pleasure Scale (SHAPS). 23 A significant improvement in anhedonia was demonstrated with Valdoxan from the first week and over the course of treatment and was greater than with venlafaxine (Figure 2). 22 Also, at the end of the study, Clinical Global Impression Scale (CGI) scores were significantly improved only in patients treated with Valdoxan. Details of the methodology and results of these two studies can be found in the article by Di Giannantonio 21 in this issue.

◆ Valdoxan demonstrates early anxiolytic efficacy even in more anxious depressed patients
Valdoxan’s anxiolytic efficacy in depression has been evaluated in this pool of three placebo-controlled, short-term studies and also in a pool of three short-term studies versus SSRI s (eg, fluoxetine and sertraline) and a selective serotonin-nor-epinephrine reuptake inhibitor (SNRI; eg, venlafaxine) over 6 to 8 weeks. 24 These three studies versus comparators were also multicenter, double-blind, randomized trials of Valdoxan for MDD and the patient population was similar, suffering from moderate to severe depression, except the study with fluoxetine.

Figure 1. Effect of 6 to 8 weeks of Valdoxan treatment on depressed mood regardless of baseline severity.
Valdoxan’s efficacy, whatever the severity of the disorder, is demonstrated by a significant difference from placebo for item 1 of the HAM-D scale, crucial for the diagnosis of depression.

Abbreviations: ∆, difference in item 1 (depressed mood) of the HAM-D scale between patients receiving placebo and those receiving Valdoxan 25-50 mg over 6 to 8 weeks; CGI, Clinical Global Impression Scale; HAM-D, Hamilton Depression Rating Scale; ITT, Intention-to-treat.

Figure 2. Snaith-Hamilton Pleasure Scale scores for anhedonia at baseline and at week 1, 2, and 8 in patients treated with Valdoxan or venlafaxine.
Valdoxan improves anhedonia early in treatment and this improvement is greater than with venlafaxine.

Abbreviations: SHAPS, Snaith-Hamilton Pleasure Scale; W, week.

tine where the patients were severely depressed with a HAM-D score $\geq 25$ at inclusion. The anxiolytic efficacy was assessed in the total population and in the more severely anxious patients (defined as those entering the study with a score $\geq 5$ in the items of the HAM-D reflecting psychic [item 10] and somatic [item 11] anxiety). The evaluation tools were the items 10 and 11 of the HAM-D and the more specific scale, the Hamilton Anxiety Scale (HAM-A).

Valdoxan demonstrated anxiolytic efficacy in depression versus placebo early in the treatment. The evaluation of the items 10 and 11 of the HAM-D scale showed a significant difference in the total population ($\Delta = 0.29; P = 0.004$) and also in the highly anxious population ($\Delta = 0.34; P = 0.005$) after 2 weeks of treatment (first evaluation) and over the course of treatment in favor of Valdoxan. The anxiolytic efficacy was independent of the concomitant use of benzodiazepines.

The efficacy in anxiety in depressed patients was also significantly greater with Valdoxan when compared with SSRIs or the SNRI venlafaxine. A meta-analysis of these studies showed that the comparison of HAM-D anxiety subscores and the decrease in the HAM-A scale was in favor of Valdoxan in the total population and even more so in the highly anxious population. The anxiolytic efficacy was independent of the concomitant use of benzodiazepines.

The German study VIVALDI corroborates in daily clinical practice the restoration of emotions induced by Valdoxan: nearly 70% of patients had improvement in their emotions after the acute treatment period (12 weeks). More recently, the effects of Valdoxan on emotions have been studied by functional imaging. Depressed patients show reduced attention to others with a shift of attention from others to self. This increased self-focus, which is a core feature in major depression, is associated with hyperactivity of prefrontal structures, such as the ventrolateral prefrontal cortex, the dorsolateral prefrontal cortex, and the dorsal anterior cingulate cortex. Depressed patients treated with Valdoxan 25 mg ($n = 13$) or placebo ($n = 12$) were scanned, as were healthy volunteers ($n = 14$), while performing self-referential processing using emotional pictures. Results demonstrate that Valdoxan has an early effect (after 1 week) in modifying functions in strategic brain areas involved in emotional processing; these changes in brain activity after only 7 days of treatment could contribute to the early clinical effects of Valdoxan.

Valdoxan’s efficacy in the three dimensions of depression

While an effect on the core symptoms of depression is an essential element of antidepressant efficacy, it is also a prerequisite for a full and sustained recovery from depression. Such a recovery implicates the restoration of emotional capacities as well as good cognitive and social functioning.

- **Valdoxan’s efficacy in helping patients to recover their emotional integrity**

Conventional antidepressants, namely SSRIs, may tend to neutralize the processing of both negative and positive emotions, and this emotional detachment that is observed during and after treatment may persist even after the clinical signs of depression have disappeared. The results obtained after administering Valdoxan to healthy volunteers, namely the specific reduction in recognition of only sad facial expressions, could suggest that treatment with Valdoxan may prevent the emotional detachment often seen with antidepressant treatment. To demonstrate this hypothesis, patients treated with Valdoxan 25-50 mg and escitalopram 10-20 mg were evaluated by means of the Oxford Depression Questionnaire (ODQ) after 24 weeks of treatment. This questionnaire investigates the prevalence of emotional side effects of antidepressants in patients with MDD. The patients evaluated were a subset of English-speaking patients (36 treated with Valdoxan and 30 with escitalopram) belonging to an international, multicenter, randomized, double-blind study with parallel groups (Valdoxan and escitalopram). Patients (males and females) had MDD of moderate or severe intensity with a 17-item HAM-D score at inclusion of $\geq 22$. Statistical analysis using descriptive statistics were carried out to compare the emotional dimension of the patients treated with Valdoxan versus escitalopram.

The results demonstrated that 60% of patients treated with escitalopram felt that their emotions lacked intensity versus only 28% treated with Valdoxan ($P = 0.063$) and that more than half of the patients treated with escitalopram (53%) felt that things that they cared about before illness did not seem important anymore versus only 16% treated with Valdoxan. This clearly demonstrated the more favorable effect of Valdoxan versus escitalopram on the emotional dimension after 6 months of treatment in the depressed.

- **Improvement in cognitive functioning**

The effects of Valdoxan in cognition were evaluated versus escitalopram in a double-blind, randomized, head-to-head study. A total of 138 outpatients with MDD received Valdoxan 25-50 mg ($n = 71$) or escitalopram 10-20 mg ($n = 67$) for 6 weeks followed by an optional treatment up to 24 weeks. Cognitive functioning was assessed by visual analog scales. After 6 weeks of treatment, Valdoxan induced more “clear thinking” ($P = 0.003$) and improved the feeling of being “wide awake” ($P = 0.005$) compared with baseline, while escitalopram did not (Figure 3).

The study VIVALDI shows again the positive effect of Valdoxan in the cognitive functioning of depressed patients, with improvement in concentration difficulties observed in 70% of these patients at the end of the acute treatment period.
Valdoxan’s unique profile of antidepressant efficacy – Muñoz

**Improvement in social functioning**

Randomized studies have demonstrated the improvement in social functioning with Valdoxan, evidenced by reduction in items 7 and 8 (“work and activities” and “psychomotor retardation,” respectively). The pooled analysis of three placebo-controlled studies with 358 depressed patients treated with Valdoxan and 363 with placebo for 6 to 8 weeks, showed a difference in favor of Valdoxan of 0.32 (P<0.001) in item 7 and of 0.2 (P<0.005) in item 8. This advantage of Valdoxan has been confirmed in the observational study VALID (VALdoxan In Depression), performed in a population of 111 depressed patients (28 were men). The study was multicenter, open, and lasted 8 weeks. The mean MADRS total score at baseline was 28.7 points and decreased statistically from the first week (24.7; P<0.001) and over the 8 weeks (9.8; P<0.001) of treatment. Patients were assessed with a specific scale, the Sheehan Disability Scale (SDS), and it was demonstrated that from the first week of treatment, the three subscores of the scale, “work/school activities,” “social life,” and “family life” were significantly improved (P<0.001). At the end of the treatment, the 3 subscores had decreased from a baseline of 7.3, 7.7, and 6.9 to 2.5, 2.4, and 2.1, respectively.15

The tolerability and safety of Valdoxan is good. Liver transaminase increases have been reported in 1.4% of patients treated with 25 mg and 2.5% on 50 mg; when Valdoxan was discontinued in these patients, the serum transaminases usually returned to normal levels. Valdoxan is contraindicated in patients with hepatic impairment. Liver function tests should be performed in all patients to ensure appropriate hepatic monitoring as recommended in Valdoxan’s summary of product characteristics.31

**Conclusion**

These data clearly demonstrate that Valdoxan has powerful antidepressant efficacy with an early impact on depressed mood, anhedonia, and anxiety. This specific efficacy on core symptoms of depression contributes to a more complete recovery of emotional integrity and of both cognitive and social functioning.

Particularly interesting is the demonstrated improvement in anhedonia with Valdoxan, as anhedonia is a core, but difficult to treat, symptom which is curiously absent from the major scales that assess depression. Valdoxan’s efficacy in reducing anhedonia occurs early in the treatment and is greater than what is seen with venlafaxine. This has been repeatedly reported by doctors and patients in real-life situations with a particular regain of interest in pleasurable activities from the first days of treatment with Valdoxan. Furthermore, CGI-scale results are more favorable for Valdoxan than venlafaxine, suggesting the importance of the improvement in anhedonia. The recent functional magnetic resonance imaging (fMRI) study sheds light on how Valdoxan regulates automatic control dur-

**Figure 3.** Changes in cognitive functioning (clear thinking) as assessed by visual analog scale after 2 and 6 weeks of treatment with Valdoxan or escitalopram. Valdoxan improved cognitive functioning better than escitalopram.

**Abbreviation:** W, week.


**Figure 4.** Change in individual items of the svMADRS at week 12 of Valdoxan treatment.

In the noninterventional study VIVALDI, 7-8 out of 10 patients experience improvement at the core of depression and in the different dimensions of depression, thus confirming in clinical practice the results of the randomized studies.

**Abbreviations:** svMADRS, shortened version of the Montgomery-Asberg Depression Rating Scale.

ing self-processing of emotions, suggesting the early set-up of the brain for long-term response and depression remission. The quality of recovery achieved with Valdoxan is the result of this efficacy and represents a unique aspect of Valdoxan. This recovery, first observed in randomized controlled trials, has been confirmed by consistent data from daily medical practice (Figure 4, page 331).13

The results presented in this article support the difference between Valdoxan and conventional antidepressants in terms of efficacy, where Valdoxan not only gives the patients the possibility to begin to enjoy life and to connect with their emotions early in the treatment, but also leads to recovery of social and cognitive functioning, which ensures a better quality of life during and even beyond depression. ■

**Keywords:** anhedonia; depression; emotions; functioning; Valdoxan

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**References**


31. Summary of product characteristics—Valdoxan (agomelatine); www.ema.europa.eu
LE PROFIL D’EFFICACITÉ ANTIDÉPRESSIVE ORIGINAL DE VALDOXAN AU CŒUR DE LA DÉPRESSION

Cet article analyse l’efficacité de Valdoxan au cœur de la dépression, c’est-à-dire sur les principaux symptômes comme l’humeur dépressive et l’anhédonie. L’humeur triste et l’anhédonie, ainsi que l’anxiété, sont courantes chez les patients déprimés et font partie des symptômes les plus pénibles de cette pathologie. Dans des études post-enregistrement randomisées et observationnelles, Valdoxan est efficace sur l’humeur dépressive et présente une activité anxiolytique précoce même chez les patients déprimés les plus anxieux. Au cours de deux études évaluant l’effet de l’anhédonie sur une échelle spécifique, la Snaith-Hamilton Pleasure Scale, Valdoxan permet une amélioration plus précoce et de meilleure qualité du plaisir et de l’intérêt, que la venlafaxine. Ces effets sur l’anhédonie ont été rapportés par des médecins et des patients en situation de vie réelle et ils sont encore plus intéressants vu la rareté des données de la littérature concernant les effets des autres antidépresseurs sur ce symptôme au cœur de la dépression. En résumé, l’efficacité de Valdoxan au cœur de la dépression permet le rétablissement de l’intégrité émotionnelle et du fonctionnement social et cognitif des patients déprimés, assurant une meilleure qualité de vie pendant et après la dépression.
Targeting emotions in the treatment of major depressive disorder is not a new idea. Since tricyclic antidepressants were first used, psychiatrists have been trying to fully understand the differences in the profiles between the various drugs, not only in terms of side effects, but also in terms of therapeutic effects. For example, is there a difference between imipramine and clomipramine? Is one or the other more apt to protect against suicidal behavior? Is one or the other more apt to provoke this behavior in some patients? Is one or the other more likely to be effective in cases of panic disorder or obsessive-compulsive disorder? Is one or the other better at diminishing impulsivity? I believe such differences exist and think that we must use this knowledge, often easy to recognize in clinical practice, but difficult to demonstrate in clinical trials.

Are positive and negative emotions connected during major depressive disorder?

For such a complex question, there is no single, simple answer. However, from one point of view, I think that two different scenarios may occur in relation to emotions during major depressive disorder, and both of them could be present to some extent in the same patient at the same time. Firstly, there is a predominance of negative emotions over positive ones. It is this scenario, the expression of negative emotions, which is most frequently recognized in depression. Even memory is affected by this valence, allowing depressive people to remember negative events in their lives perfectly, while other memories are difficult for them to recall. Secondly, patients may experience blunted emotions. This is not a new idea, for example, this incapacity to feel is rated in item 8 of the Montgomery-Asberg Depression Rating Scale (MADRS). For patients that experience this flattening of emotions during depression, selective serotonin reuptake inhibitors (SSRIs) may often maintain or even increase this “neutrality,” although improving other aspects of depressive syndrome. In this sense, negative and positive emotions could be connected in depressive patients.

What is the clinical advantage of targeting emotions in depression?

This question could be approached in two ways: based on use of psychotherapy (mainly cognitive behavioral therapy) or based on use of medications. Regarding use of medications, we must first take into account that different drugs
act in different ways; we need to take advantage of this to improve the treatment response. In general, though these differences between drugs are not evidenced by clinical trials, we must not deny their existence because we do not as yet have the means of identifying them in standard psychopharmacological clinical trials. It is usually difficult to clinically recognize and develop a consensus about subtle profile differences among drugs within the same class.

The most popular class of antidepressants is the selective serotonin reuptake inhibitors (SSRIs). We often observe patients that respond partially to these medications, while maintaining symptoms of emotional blunting. Addition of a dopaminergic medication in the treatment regimen could improve the response. Looking at this effect, it seems that we have medications that prompt people to be more phlegmatic, “British” (for example, SSRIs), and medications that allow people to be more exuberant in expressing emotions, more “Italian” (for example, bupropion). Taking this into consideration, we can help patients that seek more intensity in their feelings, for example, those complaining that they are incapable of crying in appropriate situations, which is very common.

**What does the emergence of positive feeling tell us about the recovery process?**

We have to recognize that antidepressant treatment is different from some endocrinological ones. In hypothyroidism, the use of thyroid hormone regularizes thyroid function so that it is as if the disorder were not present. Likewise, patients and even doctors often imagine that antidepressant treatment can regularize the level of brain amines to ideal levels and thus return the brain to the predepressive state. Unfortunately, that is not the case. The medication changes the patient’s emotions and behavior to such an extent that some claim antidepressants can even change the “personality” of the patient. So, the treatment must take these changes into account.

For example, we can diminish impulsivity (and emotion) using SSRIs. Indeed, for some patients this could be beneficial, but for others absolutely not. In general, an antidepressant treatment must not only remove the suffering, the guilt, and the sadness, but also restore the capacity to feel pleasure, happiness, and interest. Merely substituting absence of feelings for the suffering is not a good strategy for the patients; it is only good for the scores in scales.

**Are positive and negative emotions equally blunted after a major depressive disorder?**

Some patients can have a partial recovery after depression, treated or not. If they were treated, this partial response could be related to the medication used, as explained above.

One of the symptoms that may persist is blunted positive and/or negative emotion. At first glance, this could be viewed as an advantage for the patient, as a lack of emotion is better than suffering, but over time treatment must deal with this partial response. By contrast, ignoring this symptom (if it is a partial response) or side effect (if it is due to the antidepressant used) changes the patient’s perspectives, options, behavior, and attitude.

**Why is treatment based on targeting emotions not popular in major depressive disorder?**

Our clinical practice must be scientifically oriented. That is the reason that we have adopted evidence-based medicine and why we expend so much effort and so many resources to find evidence to justify one or another clinical decision. The problem is that we must recognize that we are not able to investigate and establish the evidence for all clinical aspects. For example, guidelines in general do not take into account comorbidities, which are very frequent in psychiatry. In regards to major depressive disorders, only now are we beginning to identify the evidence for treating clinical subtypes and the differences in the therapeutic effect of different antidepressants. It is important to remember that twenty years ago even the differences between tricyclic antidepressants and SSRIs were not recognized, although now they appear obvious. Recently, the advent of new antidepressants with different mechanisms of action has stirred up interest in whether or not those different drugs produce different therapeutic effects.

**References**


**Keywords:** antidepressants; blunted emotions; major depressive disorder; negative emotions; positive emotions
Expérience clinique du traitement des émotions dans la dépression

Il n’est pas nouveau de vouloir cibler les émotions dans le traitement de l’épisode dépressif majeur. Depuis la première utilisation des antidépresseurs tricycliques, les psychiatres ont essayé de bien comprendre les différences entre chaque médicament, non seulement en termes d’effets indésirables, mais aussi en termes d’effets thérapeutiques. Par exemple, y a-t-il une différence entre l’imipramine et la clomipramine ? L’une protège-t-elle plus que l’autre contre un comportement suicidaire ? L’une provoque-t-elle plus que l’autre ce comportement chez certains patients ? L’une serait-elle plus efficace que l’autre en cas de trouble panique ou de troubles obsessionnels compulsifs ? L’une diminue-t-elle plus que l’autre l’impulsivité ? Je crois que de telles différences existent et je pense que nous devons utiliser ces connaissances, souvent faciles à reconnaître en pratique clinique, mais difficiles à démontrer dans le cadre d’études cliniques.
Emotional dysfunction is a critical feature of disorders such as depression and anxiety, but it can be difficult to fully quantify and explore using clinical rating scales alone. In recent years, there has been significant progress in the development of cognitive paradigms to tap into different aspects of emotional processing across the domains of attention, interpretation, and memory. These approaches have been applied to characterize both the cognitive neuropsychology and the role of emotional dysfunction in depression and anxiety and to elucidate pharmacological and psychological treatment action. This article reviews different approaches for assessing emotion in healthy volunteers and in patient groups using cognitive paradigms in behavioral and neuroimaging models. These studies have revealed consistent and partly dissociable effects of depression and anxiety on emotional processing measures. Furthermore, these emotional processing markers are targeted early following administration of antidepressant and anxiolytic drug treatments. Such effects have been seen in the absence of changes in subjective experience, suggesting that they may be more sensitive measures to index emotional bias and response. This approach is a useful strategy to understand depression and anxiety and provides an experimental medicine model to test out hypotheses of treatment action and to evaluate novel compounds in development for disorders involving emotional dysfunction.

Disorders such as major depression and anxiety involve dysfunction of various aspects of emotional response and regulation. These disorders are typically diagnosed by clinical interview involving assessment of subjective experiences (for example, low mood or anhedonia). A variety of measurements exist to aid the clinician in diagnosing, monitoring, or quantifying levels of depression and anxiety. However, different clinical scales are often used in different contexts (such as primary compared with secondary care, or with psychological compared with pharmacological treatments) and may tap into slightly different aspects of depression.¹ There is increasing interest in utilizing objective measures of emotional response measured with cognitive paradigms which might also be less resistant to reporting biases or difficulty in identifying or talking about one’s own emotional experiences. Such an approach may help us understand the mechanisms underlying emotional dysfunction and its treatment.² This review will focus on the use of these cognitive paradigms to tap into different aspects of emotional processing and response and also the questionnaire and rating scale methods which may usefully complement these assessments.
Cognitive paradigms

In our day-to-day life, we are exposed to a myriad of social and emotional cues, which are often ambiguous and can be viewed from different perspectives. How we respond to this kind of emotional information is affected by what information we attend to in the first place, how we perceive or interpret this information, and what we remember later. Consistent with this idea, there is now broad experimental evidence that these different cognitive domains are affected in emotional disorders such as depression. Such evidence is consistent with cognitive models which propose that negative schema (or knowledge structures) in depression are maintained by negative biases in emotional processing, which together fuel the depression cycle. In particular, incoming information is filtered so that stimuli or events in line with the depression schema are overrepresented, leading to increased inflow and memory of negative over positive items. A similar approach has been suggested for anxiety, with information being oversampled for threat-relevant cues, thereby promoting excessive reactivity to potential threat. The existence of these biases in depression and anxiety has been widely described and characterized and has led to the development of cognitive paradigms which can tap into these different aspects of emotional processing. Such paradigms have the potential not only to inform us about the mechanisms underlying emotional disorders, but also to help us understand how different treatment approaches work to reverse this kind of emotional dysfunction.

◆ Attention to emotional information

A variety of experimental paradigms can be used to assess different aspects of attention to emotional stimuli and this review will focus on two of the most common methods: the emotional Stroop task and the dot-probe paradigm. The emotional Stroop test is a measure of interference produced by emotional content on an unrelated response. This is a variant of the classic color-naming Stroop task where participants are asked to report the color of the font in which a word is presented, but ignore the written word itself. When the color and written word are incongruent (e.g., red font for the written word “yellow”), interference effects give rise to slower responses. In a similar vein, the emotional Stroop task utilizes word stimuli with an emotional valence to interfere with the ability to make a speeded response (e.g., naming the color of the word “death”). Studies using the emotional Stroop task have demonstrated that anxiety disorders are associated with longer reaction times when naming the color of threatening words compared with neutral or positive words. Attentional biases toward emotional stimuli have also been reported in depression, although this interference effect does not seem to be restricted to depression-relevant stimuli (see meta-analysis). The emotional Stroop task also has a number of methodological caveats, which can make interpretation of the behavioral findings complex. Rather than reflecting attentional capture, it is possible that the delayed naming of the emotional words could reflect cognitive avoidance of the stimuli. In addition, interference may arise from a more generalized emotional arousal in response to the threatening or negative words, which could lead to a delay or inhibition in response selection.

An alternative paradigm which has been extensively used is the dot-probe task (Figure 1). In this task, two stimuli (typically words or images) are displayed simultaneously on a screen, in two separate locations. One of these stimuli usually has an emotional value, whereas the other one is neutral. After a brief period, the words or images disappear and a probe (for example, one or two dots) appears on the screen, either in the place of the emotional stimulus or in the place of the neutral stimulus. The volunteers are asked to indicate the position or type of probe as quickly as possible. The premise behind this task is that if attention favors the emotional stimulus, relative reaction time to detect the probe will be faster when it replaces the emotional compared with the neutral stimulus. The results from this task are less easily explained by general arousal or bias effects and it can provide a “snapshot” of attentional allocation by altering the stimulus exposure duration to enable dissection of effects on attentional capture versus disengagement.

Results from the dot-probe task suggest that anxiety is associated with relatively faster responses to probes that replace threatening stimuli than to probes that replace neutral stimuli. Again, this is suggestive of increased attentional vigilance to the location of a threatening cue (see review). As with the emotional Stroop task, such attentional biases toward threat have been demonstrated even when the stimuli are presented subliminally, suggesting that they may be operating at a relatively automatic level of processing. The dot-probe task is also sensitive to attentional negative bias in depression, which may be at least partly distinct from that seen in anxiety. While attentional bias is apparent in depression at relatively long stimuli durations (e.g., 500 ms-1000 ms), there are potential differences when the stimuli are presented for shorter durations. For example, Mogg et al reported an in-

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
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<td>BFS</td>
<td>Befindlichheits Scale</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
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<td>EPST</td>
<td>emotion-potentiated startle task</td>
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<tr>
<td>ETB</td>
<td>Emotional Test Battery</td>
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<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>HAM-D</td>
<td>Hamilton Depression Rating Scale</td>
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<td>MADRS</td>
<td>Montgomery-Asberg Depression Rating Scale</td>
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<tr>
<td>PFC</td>
<td>prefrontal cortex</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>STAI</td>
<td>Spielberger State-Trait Anxiety Inventory</td>
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<tr>
<td>vmPFC</td>
<td>ventromedial prefrontal cortex</td>
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Information processing bias can also be assessed with the affective go–no go task (a measure included in the Cambridge Neuropsychological Test Automated Battery [CANTAB]). In this task, participants are presented with a series of words which are either positive (eg, joyful), negative (eg, hopeless), or neutral (eg, element). In a given block, participants are asked to respond as quickly as possible to a given affective category and inhibit responses to the other categories, therefore providing a measure of approach, inhibition, and switching. Negative bias in this task has been shown in adult and adolescent depression, seen, for example, as quicker responses to sad versus happy stimuli, and a similar pattern is emulated following depletion of the amino acid precursor of serotonin, tryptophan, in healthy volunteers. Such effects suggest that approach and inhibition in this paradigm may model processing biases in depression.

Facial expression perception

Our ability to identify emotional states of others from rapid emotional expressions is a key aspect of social cognition which is affected in various psychiatric disorders. Depression has been associated with negative biases in the interpretation of facial expressions characterized as a relative inability to detect positive facial expressions, such as happiness and/or increased sensitivity to facial expressions displaying negative cues, such as sadness or fear. This kind of bias has been found to predict depression levels 3 and 6 months later and subsequent relapse to depression, consistent with a key role for perceptual biases in the maintenance of this disorder. Facial expression recognition can be measured by different tasks, but recent versions have capitalized on advances in computerized graphic manipulation techniques to create stimuli with different intensity levels. This morphing technique involves blending two prototype photographs of the same individual in different proportions to create a continuum between neutral expression and each emotion or between easily confused emotions, such as happiness and surprise or disgust and anger.

In the ETB, different examples and intensity levels of six basic emotions (anger, disgust, fear, surprise, happy, and sadness) are presented. Each face has been blended between the prototype emotion and neutral expression in 10% steps, which are then presented in a randomized order. Participants are asked to classify the emotional expression of each face using a labeled response box, allowing the measurement of recognition accuracy, speed of correct responses, and misclassifications for each emotion. This task is sensitive to depression and antidepressant drug administration. In particular, antidepressants such as the SSRI citalopram were found to decrease the perception of negative facial expressions (including anger, disgust, fear, and sadness) in healthy volunteers. Such effects would be expected to reverse negative biases seen in depression and reduce the impact of this key maintaining factor in this disorder. Indeed, early change in perception of facial expressions of emotion is related to the emergence of therapeutic response seen over time.

Along with other measures included in the ETB, this method has been applied to characterize novel drugs in development for depression, providing information about effects in human models, clinical profile, and dose. Using this approach, it was assessed whether the novel antidepressant agonelatine, which acts as a melatonergic agonist and 5-hydroxytryptamine receptor 2C (5-HT2C) antagonist, would also affect emotional processing despite its different pharmacological profile to conventional treatments. Consistent with this proposal,
7 days’ administration of agomelatine at 25 mg specifically decreased the recognition of sad facial expressions compared with placebo in healthy volunteers. This effect on sadness was more selective than the more generalized effects found with drugs like citalopram or reboxetine in this task, suggesting a more targeted reversal of depression-relevant processing bias following agomelatine. The use of this cognitive neuropsychological approach applied to drug development may therefore allow the dissection of different processes involved in drug action and the generation of hypotheses about antidepressant potential and application.

Emotional memory

Memory bias in depression has been well characterized, with negative stimuli being disproportionately remembered in short- and long-term memory tests in depressed patients compared with matched controls. Memory tasks used in depression typically involve explicit recall of emotional verbal material, although other more implicit measures of memory have been used, including facial affective priming and anagram solving. Self-referent stimuli may be particularly susceptible to negative bias in depression and many studies have used personality adjectives as stimuli (for example, words such as honest, original, or mean). In the ETB, a first stage of encoding is used (emotional categorization), where participants are presented with personality adjectives and asked whether they themselves would like or dislike to be referred to with each characteristic. This is a variant on an original task which asked volunteers whether each characteristic described them or not (“me” or “not me”; for example). This modification was made to ensure relatively similar response choice across groups to allow both reaction time and memory to be explored, unconfounded by differences in endorsement. This task is sensitive to negative bias in depressed patients, volunteers at high risk of depression, and dysphoric participants (unpublished data).

Effects on emotional memory may also help to dissociate those processes relevant to depression versus anxiety. In particular, the negative bias seen with explicit memory tasks in depression is not consistently found in anxiety disorders or in volunteers with high versus low trait scores on anxiety measures. Emotional memory also seems to be the domain most consistently influenced by antidepressant drug treatment. Hence, acute reboxetine, mirtazapine, and duloxetine, and repeated administration of agomelatine, reboxetine, and citalopram all increased the recall of positive versus negative stimuli in this task in healthy volunteers.

Similarly, a single dose of reboxetine was found to reverse negative bias in memory in depressed patients. Consistent with the distinction between depression and anxiety on emotional memory bias, purer anxiolytics such as diazepam do not typically affect performance on this measure, despite having action on other tasks in the battery related to anxiety (such as the dot-probe task and startle responses). Such a profile suggests again that by understanding the cognitive neuropsychology of drug action, we can start to predict treatment effects and clinical profiles to optimize randomized clinical trial assessments of novel drugs in development.

The emotion-potentiated startle task

The emotion-potentiated startle task (EPST) is a human analog of the fear-potentiated startle task used to screen for anxiolytic agents in preclinical studies. There are a number of variations in the way in which this task can be administered, but all involve electromyographic (EMG) measurement of eyeblink amplitude following a loud (eg, 90 dB) burst of noise (Figure 2). The affective component of this task is typically induced through presentation of emotive picture stimuli or through expectation of an electric shock. Increased startle reactivity has been described in anxiety and is increased following social stress. In pharmacological studies, anxiolytic drug treatments have been reported to decrease emotion-potentiated startle responses in healthy volunteer models. Thus, acute administration of diazepam and mirtazapine and 7 days’ treatment with citalo-
creased ventromedial PFC (vmPFC) responses to the same patients with generalized social phobia also showed increased amygdala responses to threatening facial expressions, but decreasing drive in the amygdala in depression would be expected to increase responses to and interest in negative stimuli and facilitate preferential encoding into memory through projections to the hippocampus. Self-referent memory tasks also tap into areas involved in self-processing, such as medial PFC and precuneus, while the emotional Stroop task activates the anterior cingulate cortex, which is involved in conflict detection and monitoring. These measures can all be adapted to work well in a functional imaging context, but the probe used most consistently across studies involves presentations of facial expressions of emotion.

Studies using this approach in functional magnetic resonance imaging (fMRI) have revealed increased amygdala reactivity to fear and/or sad facial expressions in depression, which is normalized following antidepressant treatment. These effects are seen prior to changes in mood or other symptoms of depression, consistent with the data from behavioral models reviewed above. Decreased amygdala response to negative versus positive cues can also be observed in healthy volunteer models and across different antidepressant drug classes. Further research is needed to isolate those processes, which are relevant to antidepressant versus anxiolytic properties of these drug treatments. Indeed, similar effects have also been described in the treatment of anxiety disorders. For example, a recent study by Phan et al. (2012) revealed that patients with generalized social phobia also showed increased amygdala responses to threatening facial expressions, but decreased ventromedial PFC (vmPFC) responses to the same stimuli. The vmPFC plays a key role in the regulation of emotional reactivity, presumably via its connections with the amygdala, and this pattern is therefore consistent with impaired function of this regulatory network. Of particular relevance, this imbalance in activity was normalized following a 12-week SSRI treatment.

The use of fMRI in these investigations therefore has the potential to uncover key mechanisms involved in emotional dysfunction and treatment response. However, it provides a different profile of advantages and disadvantages to behavioral testing alone. Ideally, fMRI should be complemented by behavioral results to allow any changes in neural response to be interpreted in light of evidence for impaired or affected processing in direct measures of performance. In addition, when planning a pharmacological fMRI study, it is important to be mindful of possible drug-induced changes in hemodynamic response or neural coupling, which can confound the blood-oxygen-level–dependent (BOLD) outcome measure. It is therefore important to build in appropriate control conditions and tasks to assess changes in hemodynamic response unrelated to the task of interest or to supplement fMRI assessment with more direct measures of neural activity. However, despite these limitations, the use of these neuroimaging methods has the potential to uncover key processes and mechanisms for which behavioral results are inconclusive. fMRI can therefore enhance behavioral measures of emotional processing both in our understanding of illness and its treatment and in application to drug development and screening of novel agents for depression and anxiety.

**Mood and subjective experience rating scales**

Measures of emotional bias are complemented by a thorough examination of mood and subjective experience, based on self-report or clinician-rated scales. To assist in diagnosis and provide a measure of illness severity, the clinician-rated 17-item Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) have been well validated for use in clinical trials and research studies. The self-report measures such as the Beck Depression Inventory (BDI) and the Patient Health Questionnaire-9 also provide highly relevant information, with the latter being used as a diagnosis aid in primary care settings. However, it should be noted that although each scale provides an overall measure of depression, the emphasis on different symptoms seen in this disorder is different. In example, the HAM-D has a greater number of items relating to sleep and anxiety than the MADRS or the BDI, whereas the BDI places more emphasis on pessimism and feeling of guilt. It is therefore important to consider the different symptom clusters in depression which might be relevant to a dissection of the cognitive neuropsychological maintaining factors.

In addition to rating scales of depression and anxiety, which typically ask about symptoms and experiences over a period of one or two weeks, it is also necessary to have measures of current mood state which may be more responsive to pharmacological induced change in healthy volunteer groups. Again, a variety of measures exist to monitor different aspects of everyday subjective state. The positive and negative affective schedules provide information across a period of time set by the experimenter (ie, over the last week or day or hour) with two subscales detailing positive and negative experiences. The Befindlichkeit Scale (BFS) is widely used in conjunction with the ETB to provide a measure of change in mood.
and energy levels.46 This requires the volunteer to choose between two adjectives (eg, shy or bold, sluggish or animated) describing current state and therefore may be more sensitive to minor changes in state than symptom-based measures. Anxiety can be assessed by the Spielberger State-Trait Anxiety Inventory (STAI), which provides two measures, a measure of phasic (or state) anxiety response in a given situation and a trait measure of more stable patterns of anxiety across time.47 The STAI has been used across studies to recruit volunteers with high or low levels of trait anxiety and to index the response to stressors and pharmacological manipulations. Finally, visual analog scales are used widely in the field of pharmacological challenges to monitor side effects and key effects on mood.48 These involve the presentation of a line (typically 10 cm) with a description at the top (eg, alert) and labels at each end (running from “Not at all” to “Extremely”). Volunteers are asked to mark a place on the line which represents how they feel in relation to the descriptor. These can be used repeatedly within the same experimental setting and therefore provide a more finely grained analysis of subjective state, which can be applied in healthy volunteers and patient groups.

**Conclusions**

Emotional processing can be measured using objective measures of cognitive function both in behavioral and neuroimaging models. These have been used to explore the underlying etiology and treatment of emotional disorders, such as depression and anxiety. Emotional processing is affected earlier in treatment than changes in subjective experience and these early effects are predictive of clinical action occurring later in time. This approach may therefore be more sensitive to change than measures of subjective state and provide an early marker of response for treatment studies. Objective performance on cognitive tests is also less likely to be affected by reporting bias or difficulty of accessing relatively implicit cognitive-emotional states. The application of this kind of approach to complement diagnosis of emotional disorders, in addition to treatment response, represents an exciting possibility for future studies. Together with clinical and nonclinical assessment of mood, anxiety, and experience, this approach can be used to reveal key aspects of emotional dysfunction and to understand how established and candidate treatments may work to treat these disabling conditions.

**References**


Keywords: anxiety; cognitive neuropsychology; depression; emotion; emotional processing

ÉVALUATION DE L’ÉMOTION

La dysfonction émotionnelle est un aspect essentiel des troubles de l’anxiété et de la dépression mais qui peut être difficile à explorer et à quantifier pleinement à l’aide des seules échelles cliniques d’évaluation. Des progrès significatifs ont été réalisés ces dernières années dans le développement de paradigmes cognitifs permettant d’évaluer de manière précise et discriminative la dysfonction émotionnelle tant sur le plan de la neuropsychologie cognitive que sur celui de son rôle dans la dépression et l’anxiété, ainsi que pour comprendre l’action thérapeutique psychologique et pharmacologique. Cet article passe en revue les différentes méthodes d’évaluation de l’émotion utilisées dans des études chez des volontaires sains et dans des groupes de patients à l’aide de paradigmes cognitifs appliqués à des modèles comportementaux et de neuro-imagerie. Ces études ont révélé des effets constants et en partie dissociables de la dépression et de l’anxiété sur les indicateurs mesurés du processus émotionnel. Ces indicateurs, en outre, sont ciblés de façon précise au cours de l’administration de traitements anxio-lytiques et antidepressifs. De tels effets ont été observés en l’absence de modifications de l’expérience subjective, ce qui suggère que ces indicateurs seraient plus sensibles pour indexer les biais et les réponses émotionnelles. Cette approche constitue une stratégie utile pour comprendre la dépression et l’anxiété ainsi qu’un modèle médical expérimental pour tester des hypothèses d’action thérapeutique et évaluer des molécules nouvelles en développement sur les troubles comportant une dysfonction émotionnelle.
This review focuses on the links between the emotional brain and the social brain through analysis of the role of the amygdala. The amygdala is believed to have a key role in detection of salient and personally relevant stimuli in concert with other regions of the emotional brain. Among salient stimuli, social signals are potent sources of emotion as they indicate self-relevant information in the environment. We describe the role of main neurotransmitters—serotonin, norepinephrine, and dopamine—on amygdala activity and we emphasize the role of oxytocin in social function. Evidence from brain imaging studies show that oxytocin may regulate the salience of social signals through modulation of amygdala activity.

Emotions are defined as episodic and synchronized changes in physiological, behavioral, and cognitive responses of the organism, reflecting the identification of salient stimuli in the environment. Emotional episodes are critical to survival and have a strong and persistent influence on cognitive processes such as perception, attention, memory, and decision-making. Accordingly, with this persistent relationship between cognitive and emotional processes and the putative dysfunction of these processes in psychiatric disorders, there is a growing interest in the study of the neurobiology of emotion. In this paper, we will focus on findings about the neuroimaging and neurochemistry of emotion with a special emphasis on the links between emotion, social behaviors, and the amygdala.

Emotional brain and social brain

Animal studies, brain lesions in human, and more recently, neuroimaging studies have contributed to the definition of the so-called “emotional brain.” The emotional brain is a highly distributed set of cortical, subcortical, and limbic regions organized into several subsystem networks (Figure 1).1,2

The emotional perception network is composed of cortical and subcortical structures, including sensory cortices, and the amygdala, anterior cingulate cortex, insula, basal ganglia, and orbitofrontal cortex. This system is associated with the detection and evaluation of emotional stimuli.

The emotional regulation network comprises the ventro- and dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, the dorsomedial prefrontal cortex, the posterior cingulate cortex, the precuneus, and the hippocampus. These regions are
involved in contextualization of emotion and emotional regulation, the ability to dampen or increase response to emotional stimuli. A subset of these regions (ie, medial prefrontal cortex, hippocampus, posterior cingulate cortex, precuneus) constitutes the default-mode network (DMN). The DMN has been related to prospection, autobiographical memory, self-referential processing, and theory of mind, a common set of cognitive processes devoted to projecting oneself into worlds that differ mentally, temporally, or physically from one’s current experience.

Several stimuli can activate the emotional brain. Among these stimuli, social stimuli such as faces, persons, or social feedback (ie, social criticism or approbation) are major sources of emotion. It is now well admitted that there is a large overlap between the emotional brain and the social brain. 3

The amygdala and processing of self-relevant stimuli

Major evidence for such overlap between the emotional and the social brain comes from studies on the amygdala. The amygdala is a major component of the emotional perception network and it receives input from the sensory cortices and thalamus. The amygdala has strong reciprocal connections with other regions of the emotional brain, such as the ventromedial prefrontal cortex and the orbitofrontal cortex. Moreover, the amygdala has widespread projections to the basal forebrain, striatum, nucleus accumbens, hippocampus, and sensory cortices. 4

The amygdala is usually associated with fear processing and is involved in threat detection and fear learning. 5,6 Brain imaging studies have challenged the specific role of the amygdala in fear processing by showing that both negative emotion and positive emotion activate the amygdaloid complex. 7

The amygdala is also sensitive to social signals, such as faces, gaze direction, intention, and trustworthiness. 8 Consistent with a putative role of the amygdala in social processes, patients with amygdala lesions showed not only abnormal fear response, but also impaired social behaviors. Amygdala lesions are associated with increased social approach and difficulties to monitor interpersonal distance. 9 Likewise, mental disorders with major social impairment such as autism and schizophrenia show abnormal functioning of the amygdala, characterized by increased reactivity in response to social stimuli.

Social signals and self-relevance

The detection, monitoring, and evaluation of social signals are essential for individuals to navigate the social world and social signals may indicate the presence of self-relevant stimuli in the environment. For instance, negative social signals, such as social exclusion, are associated with intense emotional responses and behavioral changes. To be socially excluded is to be rejected, ignored, or devaluated by others. Social exclusion may result from several social situations including, for instance, forced separation from a loved one, loss of a job, or being ostracized or criticized. Most people have experienced episodes of social exclusion in their lives.

A seminal functional magnetic resonance imaging (fMRI) study has illustrated that social exclusion literally induces psychic pain with activation of the ventrolateral prefrontal cortex, anterior insula, and anterior cingulate cortex, regions classically
involved in physical pain. In this study, the authors used a Cyberball paradigm, in which participants were led to believe that they were participating in a ball game with real individuals over the Internet, whereas the actions of the other two players were preprogrammed to exclude the participant after a few throws. Several studies have replicated these results on social exclusion and a recent meta-analysis by our group (Roitg et al, in preparation) showed that social exclusion induced by the Cyberball task mainly activates the subgenual cingulate cortex, a region involved in the production of negative emotion and the pathophysiology of major depression.

Social exclusion has a profound psychological and physiological impact, as it threatens fundamental human needs, such as sense of self-esteem, sense of belonging, meaning of existence, and sense of control. On a cognitive level, social exclusion may dampen self-esteem, which, according to the socio-meter theory, is a gauge that measures the quality of people's relationships with others and alerts the individual to the possibility of social exclusion. Consistent with this formulation, in a recent fMRI study in which subjects received feedback from peers on how they were liked or disliked, Somerville et al showed that the level of self-esteem modulated reactivity of the ventromedial prefrontal cortex and amygdala to positive and negative social feedback. Decreased self-esteem induced by social exclusion may affect self-evaluation and increase self-focused attention (“Am I liked? Why don’t others like me?”). The by-product of self-evaluation may subsequently increase people’s need to pay more attention to others in order to detect self-relevant stimuli and to reconnect with others.

Overall, this emphasizes the importance of social inclusion and social acceptance for emotional well-being.

Neuropharmacology of emotion

The discovery of drugs such as imipramine and iproniazid, which elevate mood in patients with depression, revolutionized the treatment of mood disorders. Antidepressant drugs and their mechanisms of action on two principal neurotransmitters, ie, serotonin and norepinephrine, contribute to the development of research on the chemistry of mood and emotion.

Beyond their abilities to correct depressive symptoms in patients with major depression, antidepressants modulate the processing of emotional stimuli in healthy subjects. In a seminal study, Harmer et al showed in healthy volunteers that a single dose of the selective serotonin reuptake inhibitor (SSRI) citalopram enhanced the recognition of happy and fearful faces. One-week administration of the same drug in healthy volunteers facilitated the processing of positive emotional information with a better memory for self-related positive personality traits. In this study, the authors used a memory task where subjects encoded positive and negative personality traits while making a self-referential judgment on these words. Citalopram also induced a decrease in recognition of negative facial expressions. The short-term emotional effects of citalopram occurred without any changes in mood. Several studies have replicated these findings with other SSRIs or using different antidepressant drugs with different mechanisms of action. For instance, reboxetine, a selective norepinephrine reuptake inhibitor, and venlafaxine, a serotonin-norepinephrine reuptake inhibitor showed slightly similar effects on emotion processing in healthy subjects. According to a recent review, serotonergic agents may target negative emotion whereas noradrenergic agents target positive emotion.

Harmer et al have suggested that pharmacological antidepressant interventions and manipulation of serotonin and/or norepinephrine may exert their therapeutic effects through the correction of emotional biases of depression. Two emotional biases have been described in major depression: (i) the tendency to prioritize the processing of negative emotional stimuli and (ii) increased self-focus, the tendency to relate to one’s self emotional or neutral stimuli. The early correction of these emotional biases and exposure to environmental stimulation would over time and experience reduce depressive symptoms. This effect of antidepressants, such as SSRIs, on the processing of emotion mirrors the effect of serotonin depletion on sadness.

In both healthy and depressed patients, self-focus involves the medial prefrontal cortex, whereas the processing of negative information mainly involves the amygdala. SSRIs in healthy subjects modulate the medial prefrontal cortex and amygdala regions, an effect consistent with the distribution of serotonergic receptors in limbic pathways.

There is renewing interest in the effects of antidepressants on anhedonia, a loss of positive emotion and a core feature of depression. It is now well established that dopamine is associated with reward processing and learning. Long-term treatment with nearly all antidepressants increases responsiveness to dopaminergic stimulation, perhaps due to enhanced signaling through dopamine D₂ or D₅ receptors. However, it has been suggested that long-term treatment (ie, more than two months) with an SSRI may induce a blunted response to positive and negative emotional stimuli, likely explained by dopamine depletion.

Agomelatine is a new antidepressant and a potent agonist of melatonergic receptors MT₁ and MT₂ and an antagonist of the serotonin 2C (5-HT₂C) receptor. This antagonistic action on 5-HT₂C receptors facilitates dopamine release in the prefrontal cortex, without effect on extracellular levels of serotonin, indicating that agomelatine may show selective effects on positive emotion. It has also been demonstrated recently that the melatonergic part of agomelatine is necessary for the enhancement of dopamine neurotransmission. In healthy volunteers, Harmer et al showed that 7 days’ administration of agomelatine improved memory for self-encoded positive emo-
The hedonic component of reward at the time of delivery of rewarding stimuli involves endogenous opioids. Endogenous opioids are a family of neuropeptides including endorphins, enkephalins, dynorphins, and orphanin FQ, as well as their various receptor subtypes. Oxytocin (OT) modulates several hormones. For instance, dopamine, epinephrine, serotonin, and dopamine. We have discussed how endogenous opioids modulate behavioral responses to emotional and social stimuli, such as direct gaze compared with aversion. Moreover, OT increases gaze to the eye region of human faces, an essential feature to detect and identify emotion. Finally, OT improves memory for faces, with a bias for happy faces, which facilitates the establishment of social memory and links.

Faces are a special category of visual stimuli that induces social approach or social withdrawal. By attenuating amygdala activity in response to negative facial expression, OT may allow more accurate appraisal of social signals and promote social approach. This is consistent with results from studies with neuroeconomic paradigms and economic games demonstrating that intranasal OT increases trust and abnormal acceptance of betrayal behavior. It is beyond the scope of this review to discuss evidence on the unique role of OT in social affiliation and attachment. However, we want to mention here that OT influences emotional responses and behaviors following social rejection. Thus, in two studies with the Cyberball task, subjects receiving intranasal OT had normal emotional responses to social exclusion, but showed an increased desire to reconnect with others and demonstrated increased helping behaviors. Overall, the prosocial and positive emotional biases induced by OT put emphasis on the therapeutic potential of this neuropeptide in mental disorders marked by emotional and social impairment.

**Conclusion**

The emotional brain has evolved to process salient stimuli in the environment. Within the emotional brain, the amygdala structure plays a major role in the detection of social stimuli that signal self-relevant and important information in the environment. Many antidepressants regulate the activity of the amygdala through modulation of the neurotransmitters norepinephrine, serotonin, and dopamine. We have discussed the role of neuropeptides such as OT in social behavior. OT, by regulating the response of the amygdala to social signals, induces positive emotional bias and promotes prosocial behaviors. OT activity is associated with activity of dopamine neurotransmitters, suggesting the complex interplay between neuropeptides and neurotransmitters for regulation of emotion. The studies of chemistry and neuroanatomy of emotion will contribute to unravel the functional architecture of the social and emotional brain. These studies will highlight the role of new pathophysiological pathways in mental disorders and will help to define new treatments.

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Cet article examine les liens entre le cerveau émotionnel et le cerveau social en analysant le rôle de l’amygdale. L’amygdale a probablement un rôle clé dans la détection des stimuli principaux et individuels pertinents en coopération avec les autres régions du cerveau émotionnel. Parmi les principaux stimuli, les signaux sociaux sont des sources puissantes d’émotion car ils donnent une information auto-pertinente dans l’environnement. Nous décrivons le rôle des principaux neurotransmetteurs, sérotonine, noradrénaline et dopamine, sur l’activité de l’amygdale et nous insistons sur le rôle de l’ocytocine dans la fonction sociale. Les études d’imagerie cérébrale montrent que l’ocytocine peut réguler l’importance des signaux sociaux en modulant l’activité de l’amygdale.

**Keywords:** amygdala; emotional brain; neuropharmacology; oxytocin; self-relevance; social brain; social signals

**Neurobiologie et neuropharmacologie de l’émotion**

**Cet article examine les liens entre le cerveau émotionnel et le cerveau social en analysant le rôle de l’amygdale. L’amygdale a probablement un rôle clé dans la détection des stimuli principaux et individuels pertinents en coopération avec les autres régions du cerveau émotionnel. Parmi les principaux stimuli, les signaux sociaux sont des sources puissantes d’émotion car ils donnent une information auto-pertinente dans l’environnement. Nous décrivons le rôle des principaux neurotransmetteurs, sérotonine, noradrénaline et dopamine, sur l’activité de l’amygdale et nous insistons sur le rôle de l’ocytocine dans la fonction sociale. Les études d’imagerie cérébrale montrent que l’ocytocine peut réguler l’importance des signaux sociaux en modulant l’activité de l’amygdale.

**Keywords:** amygdala; emotional brain; neuropharmacology; oxytocin; self-relevance; social brain; social signals
Vienna, the glittering capital of the Habsburg Empire, was in decline at the end of the 19th century. Yet it remained hailed as the “Mecca of medicine,” thanks to the likes of Rokitansky, Virchow, and Freud. Three artists offer a controversial interpretation of that period: Messerschmidt, with his strangely modern sculpted “Character Heads,” Klimt, with the much-decried eroticism that pervaded his monumental allegory of Medicine, and Schnitzler, who satirized the Viennese medical establishment in his works.

Medical developments in the 19th century: the Vienna Clinical School

I. Percebois, France

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Emoticons in marble and bronze: Messerschmidt’s intriguing “character heads”

P. Poullalié, France

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In the 19th century, the heart of medical science beat strongest in Vienna, described by the anatomist Rudolf Virchow as “the Mecca of medicine.” Its university exerted international influence thanks to talent drawn from all corners of the Habsburg Empire. This period was the high point of the Second Vienna School, personified by Carl von Rokitansky and Josef Škoda, who drilled the imperial capital in the doctrine of “therapeutic nihilism.” Their approach sought to reinvent medical knowledge from the bottom up. It went hand in hand with a distrust of the pharmaceutical remedies available at the time, which they dismissed as ineffective. Although they attracted criticism and were accused of favoring science over their patients, Rokitansky and Škoda were the key contributors to the School’s renown, along with Theodor Billroth who laid the foundations of modern surgery in the city. But Vienna offered little welcome to certain other innovators, forcing Franz Anton Mesmer, the inventor of animal magnetism, into exile, attacking the work of Sigmund Freud, the father of psychoanalysis, and driving Ignaz Semmelweis, the founder of hospital hygiene, to an early death. Spanning the spectrum between light and darkness, Viennese medicine was also an inspiration to writers and artists, in particular to the former doctor Arthur Schnitzler, and a recurrent reference for the paintings of Gustav Klimt. Pioneering, bold, and riven by scandal, the Second School made Vienna the scientific capital of Mitteleuropa.
As the capital of the Habsburg Empire, Vienna was the de facto capital of 19th-century Europe, playing host in 1814 to the monarchs and diplomats tasked with drawing up a new geopolitical order after Napoleon’s defeat. The entire world looked to this Mitteleuropa city that stood center stage in the political arena up to the First World War and the collapse of the Austro-Hungarian Empire: “For one century, more than ever, the history of Central Europe was reflected in that of this city which commanded its fate.”

The Vienna of the time exerted unprecedented influence as the embodiment not only of the artistic avant-garde, but also of scientific progress, thanks to its renowned university. Its star shone with a special brightness in medicine, to the extent that none other than the Berlin anatomist Rudolf Virchow labeled it the “Mecca of medicine.” The pagan Mecca, visited by pilgrim physicians from all over the world, played host to a succession of the most eminent practitioners of modern medicine.

The “Mecca” of medicine

From therapeutic nihilism to major strides in morbid anatomy and surgery

Viennese medicine reached a pinnacle in the 19th century. It was the embodiment of the Habsburg Empire and drew its strength from the Empire’s multicultural base. Its leading figures—those writ large in its history—converged on the capital from the four corners of the Empire to endow the School of
The Viennese medicine of the 19th century excelled not only in its technical prowess and innovations, but also in its ideology, which became so characteristic of its practitioners that it served as their signature. Known as therapeutische Nihilismus (therapeutic nihilism), the method defined the Second Vienna School under the leadership of Carl von Rokitansky and Josef Škoda. The First School had laid the foundations of the method at the end of the 18th century thanks to the reforms of Gerhard van Swieten and the emphasis on diagnosis. The influence of Schopenhauer’s Naturphilosophie was also visible in the deep skepticism expressed by the Viennese physicians toward the pharmacological treatments available at the time. Instead, they advocated nonintervention, trusting in Nature’s powers of recovery. This shifted the therapeutic vocation of medicine temporarily into the background, in favor of an overriding concern to first understand how the human body worked before seeking to heal it. The words of Józef Dietl, a pioneer urologist and fervent advocate of therapeutic nihilism neatly sum up the change in emphasis: “While the old school carried on therapy before engaging in research, thenew school began researching in order to be able to understand therapy… Our strength lies in knowledge, not in action.”

Up until the final page of this text, there are no further pages included in the document. The text ends with a reference to Sir Arthur Conan Doyle, the Father of Sherlock Holmes, who studied medicine in Edinburgh and later wrote a thesis on tabes dorsalis (syphilis) and studied ophthalmology in Vienna in 1890. The image of an anatomical model from Florence (1754-1814) is noted as being created by Clemente Michel-Angelo Susini and commissioned by Emperor Joseph II. The wax models were carried to Vienna and are still exhibited at the Museum of the Medical University of Vienna. The image of Sir Arthur Conan Doyle is noted as being taken in 1930.
Age of Enlightenment, diagnosis had been based mainly on Hippocratic signs and symptoms. In the 19th century, it was dethroned by the modern science of morbid anatomy that introduced radical change by shifting the physician’s gaze from the bedside to the autopsy room. Rokitansky was said to have performed around 85,000 autopsies by 1844 when a chair of morbid anatomy was established in Vienna.

The names of Viennese physicians live on in eponymous conditions such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (Müllerian agenesis) in gynecology. But at the time, they were celebrated primarily for their doctrine of therapeutic nihilism, as described by William M. Johnston in *The Austrian Mind:* “by 1850 skepticism toward traditional therapy had so taken root that the only medicament used in the General Hospital was cherry brandy. For fear of distorting symptoms, doctors refused to prescribe any remedies.” It may be surprising that the most eminent specialists should have concentrated less on the patient than on building up a body of knowledge, but their approach served the purpose of medical progress as it sought to shake off the traditional remedies that had been in use for centuries with nothing but unquestioning belief in their favor: “A profusion of clinical evidence, including the rarest maladies, encouraged Vienna’s physicians to exploit observation as a tool for exploding medical myths.” However, even in the 19th century, the proponents of therapeutic nihilism themselves came under attack, in particular from two celebrated figures: the biologist Ernst Haeckel and physiologist Hermann Helmholtz. The latter was scathing in his criticism of the cruelty of Josef Škoda, whom he accused of instrumentalizing patients for the greater good of science: “And one degraded the patient who was, after all, a human being, and disgraced him, as if he were a machine.” Even foreign observers were taken aback by his insensitivity, as shown in the *Journal de Médecine, de Chirurgie et de Pharmacologie* published by the Brussels Society of Medical and Natural Sciences in 1858: “Rarely, if ever, has medicine seen as absolute or as fervent a doubter… On the 28 sick in his care—or rather on his long-suffering patients—he deploys a succession of all the most traditional and vaunted medicines, and do you know to what end… With the sole intention of demonstrating to his students that all these medicines are in every case completely ineffective.”

Although therapeutic nihilism came to be called into question in the second half of the century, it remained intimately associated with the Vienna School, characterizing the fields not only of clinical medicine and morbid anatomy, but also of surgery, whose undisputed champion was Theodor Billroth. According to the father of modern surgery, “reliance on excising a diseased part accorded with stress on pathological anato-

*Stages of gastric resection, by Christian Billroth (1829-1894)* who carried out the first successful ablation of gastric cancer in 1894. Paradoxically, advances in surgery were a direct consequence of “therapeutic nihilism.” © Wellcome Library, London.

*Surgeon binding up woman’s arm after bloodletting.* Oil painting (50.4 x 39.9 cm, on copper) by Jacob Toorenvliet (1666). Probably the most popular form of treatment for centuries, Joseph Dietl (1804-1878), one of the fathers of “therapeutic nihilism” waged a successful battle against the then prevalent recourse to bloodletting as cure for pneumonia. © The Wellcome Library, Wellcome Images.
Anton Mesmer (1734-1815) exercising his hypnotic skills (right), while patients try out the effects of his famed “tub” or “baquet” (no, it’s not a table!). This was a oak tub containing iron filings that delivered “magnetic rays” which Mesmer claimed would cure any number of ailments. Engraving, 1780. Bibliothèque Nationale de France. © akg-images.
Billroth. Although he too went through a period of therapeutic nihilism in his youth while training in the various departments of Vienna’s General Hospital, he was to develop his approach to the treatment of mental disorders in opposition to the prevailing orthodoxy. At a time when psychiatric patients were condemned to trepanation or to confinement in the Fools’ Tower, Freud’s preference for a talking cure over the trephine led to him being outcast by his colleagues.

His fate bears astonishing resemblance to that of Mesmer in that it was in Paris that he too sought refuge from the sustained hostility. In Vienna, Freud’s professor Theodor Meynert, who headed the department of psychiatry, looked down on his work, whereas in the Parisian medical world, Freud found fresh prospects beckoning. In 1885, he trained in hypnosis under Jean-Martin Charcot at the Salpêtrière Hospital and began translating his works for the benefit of his compatriots. Yet when he returned to Vienna the following year and presented a report on male hysteria to the society of physicians, he found himself once again the butt of criticism and ridicule. As a man of science, he experienced frustration on two levels: not only were his innovative theories treated with scorn, but he was kept pinned down to the post of Dozent, unable to advance higher up the university ladder. Freud also took it as evidence of the anti-Semitism rife throughout the Medical School, scathingly portrayed on stage by Arthur Schnitzler in Professor Bernhardi, and that was eventually to drive him into exile in 1938.

Freud managed to survive Vienna and his colleagues’ hostility, but not everyone in the 19th century was so lucky. Despite revolutionary discoveries that were to transform clinical practice and the history of medicine, Ignaz Semmelweis fell victim to the city. His fate was sealed in 1846 when as a young master of surgery he joined Professor Johann Klein’s department of obstetrics at the General Hospital. He was astonished to observe that the mortality of young mothers was much higher in this department than in the adjoining department of Professor Bartsch. He eventually worked out why. After various experiments, he established that it was the medical students training under Professor Klein who were passing fatal infections on to the patients: by going straight from the autopsy room to the labor ward, they were spreading the puerperal fever that caused the young mothers to flee the hospital, sometimes...
even to deliver in the street. By making the students wash their hands in chlorinated lime solution, Semmelweis significantly decreased the mortality rate. Yet his colleagues remained skeptical and maintained that his handwashing protocol was too restrictive in practice. But in reality, just as with Mesmer and Freud, Semmelweis was challenging the doctrine of therapeutic nihilism, thereby blocking all hope of future promotion. Even the support he received from his fellow Hungarian, Josef Škoda, proved of no avail in preventing his disgrace.

Following this bitter failure, Semmelweis left Vienna for Budapest, entrusting his colleague Professor Ferdinand von Hebra with the job of publishing his research in the Journal de la Société Impériale et Royale de Médecine, which the professor duly did, not without some errors. It was only in 1861 that Semmelweis himself put pen to paper to lay the foundation of modern aseptic technique in his book Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers (Etiology, concept and prophylaxis of childbed fever). In 1862, in an open letter to professors of obstetrics in Vienna, he gave vent to his anger and bitterness: “I would be committing a crime if I kept silent any longer and did not publish the results of my experience. I have the intimate conviction that since 1847 thousands of women and children have died who would still be alive had I not kept silent.” Semmelweis succumbed to depression and mental illness before dying in 1865 in an asylum close to the city of Vienna that had rejected him. Modern history books often refer to Semmelweis as a “Viennese obstetrician,” but it is important to remember that he paid for this title with his life.

**Medicine in Viennese art and literature**

**Gustav Klimt and his ill-fated university mural Medicine**

Vienna was without doubt one of the cultural capitals of 19th-century Europe, standing at the forefront not only in science, but also in literature in the shape of the Jung-Wien (Young Vienna) group and the graphic arts represented by the Sezessionsstil (Vienna Secession) movement. As the bedrock of Vienna’s reputation, medical science also permeated the arts, as shown in the early work of Gustav Klimt, who epitomized art nouveau and the Vienna Secession. In 1888, Klimt started work on a portrait of Carl von Rokitansky for a painting of the Burgtheater auditorium, famous for having premiered at least three of Mozart’s operas. This was officially commissioned by the Vienna city council with a view to immortalizing the old theater before its replacement. In this painting for which he was awarded the Emperor’s Prize, Klimt portrayed the capital’s leading figures in such a striking gallery of characters that “everyone in high society fought for a place in the group portrait.” Behind the silhouette of Rokitansky, Gustav Klimt paid tribute to Viennese medicine as a whole; by removing the anatomist from the dissection room and plunging him into a high society setting, he lifted science out of the University to share in its splendor.

Medical science was also intertwined with a key moment in Klimt’s career in so far as his early work on the Ringstrasse interior led to him being selected in 1896 to paint the ceiling of the Great Hall of the University. This commission marked the consecration of Klimt, but caused scandal within the sacrosanct Viennese institution. The history of this abortive work is that of a vision, for which only some preparatory drawings now remain, testimonies to the power of Klimt’s art in this period. The vision originated in 1900, when Klimt exhibited Philosophy, the first of the three compositions commissioned for the Great Hall. The university authorities were expecting a classical work. Instead, Klimt represented philosophy as an enigmatic female sphinx surging out of a star-lit sky. The symbolist style of this painting unsettled the general public, but the scandal only increased when Klimt delivered his second composition, entitled Medicine, at the Vienna Secession exhibition in 1901. In this painting, the Greek goddess of health Hygieia stands disdainful before the onlooker, brandishing the phallic symbol of a serpent. Reinforcing the eroticism of the scene is the presence, opposite the entwined shades of the sick and dying, of a sensuously pregnant woman whose flagrant nudity appeared profoundly shocking to the conservative professors. These reactionary forces organized an anti-Klimt cabal that recruited popular scientific periodicals such as the Medizinische Wochenschrift to exert pressure on the city authorities and have the official commission cancelled. Yet Klimt managed to capture the very essence of Viennese medicine in this painting, with its intimate juxtaposition of death and life, and its transformation of the gruesome autopsy room into a place of serious study. However, Medicine was never to find a home in the University, any more than Philosophy or Jurisprudence. In the late 1930s, all were seized from their Jewish owners and moved for protection to Immendorf Castle, which was set alight in 1945 by retreating SS, in final and uninhibited consummation of the professorial condemnation half a century earlier.

**Arthur Schnitzler: a doctor fictionalizes Viennese medicine**

In Vienna, art thus interacted with medicine. Artists regarded the men of science with an eye that was both admiring and critical, a duality particularly apparent in the writings of Arthur Schnitzler, whose approach was not dissimilar to that of the Vienna Secession master in that he too sought to “expose

Left page: **Gustav Klimt (1862-1918) was commissioned to paint three ceiling murals—the University Paintings—for the Great Hall of the University of Vienna: Philosophy, Medicine, and Jurisprudence.** "Medicine" was presented in March 1901 at the Tenth Secession Exhibition. The goddess Hygieia (middle, bottom) holds the snake of Asclepius and a cup with water from the river Lethe in Hades. Above her, a laughing skeleton clutches the corpse of a woman shrouded in dark muslin. A column of nude figures extends on the right symbolizing life, while a provocatively exposed nude woman is featured on the left, with a newborn infant at her feet. "Medicine" and the two other ceiling paintings, judged "pornographic," were never displayed on the ceiling and were eventually destroyed by retreating German troops in May 1945 at Immendorf Castle, Lower Austria. 430×300 cm. Photo and ©: Archive Leopold Museum, Vienna.
The erotic depths beneath Viennese Phaeaceanism. To understand the scientific character of this Young Vienna writer, we need to go back to his upbringing in the shadow of his father. As one of Vienna’s most celebrated laryngologists, Johann took a poor view of his son’s literary inclinations and forced him to complete his medical education. In his autobiography, Schnitzler was to complain of the stifling aridity of the medical curriculum. He described the internal conflict besetting a young student, or rather budding author, torn between pen and scalpel: “I was undecided and vacillating, and these were my feelings about medicine too. Being forced to study medicine... at times aroused in me a particularly violent repulsion towards it, while at other times drawing me to it and moving me to the very roots of my being.” In May 1885, Schnitzler qualified as a doctor and used his talents to help his father in Vienna’s Poliklinik. When several years later he decided to give up his medical career, he found it impossible to detach himself from the medical environment that he knew so well and was to carry over into his fiction.

One reason why Viennese medicine is so central to Schnitzler’s work is that he was describing its golden age, even to the extent of prefiguring Freudian psychoanalysis. He drew inspiration from his experience of medicine and enjoyed blurring the frontier between autobiography and fiction by subtitling some of his early stories, such as Mein Freund Ypsilon (1887), “Pages from a doctor’s notebook.” He thus drew his readers into a tantalizing web of masks and doubles, depicting himself under a variety of fictional avatars, such as Dr Merano in Die Weissagung (1902). The stories resemble consulting rooms in which the reader eavesdrops on a series of psychological disturbances and mental illnesses. In Der Sohn (1889), for example, Schnitzler studied the origin of certain neuroses, in the person of a dying mother who attempts to explain the violent behavior of her son by admitting she had tried to kill him when he was a child: “Do we conserve blurred memories from the first hours of our lives that we have become unable to interpret but that do not disappear without leaving a trace?” His writing reflects the influence of his mentors, in particular his professor, the psychiatrist Theodor Meynert. Despite feeling a certain antipathy for the man, Schnitzler owed him his fascination with dreams and hypnosis. This also accounts for the close relationship between his writings and the work of Sigmund Freud, who had also been Meynert’s student and considered Schnitzler his Doppelgänger.

Schnitzler’s style was all about stripping his characters bare and studying their psyche. He was a master of the internal monologue which he used to expose inner conflicts to the reader’s gaze. He resorted to the same technique to handle the subjects of death and loss of a loved one. These represent a leitmotif in his work, in particular in Ein Abschied (1896) and Die Toten schweigen (1897), two complementary short stories that together form a veritable case history. However, even as he retained his physician’s eye, Schnitzler never used medical science as a pretext for long disquisitions, but only as a plot driver: “he never sought to impress with the superiority conferred upon him by his medical skills.... Almost always a simple allusion would suffice to illuminate the story, without weighing it down or inserting blunt or unprepossessing details.”

Thus, his short stories, novels, and plays were not texts of medical vulgarization, but snapshot reconstructions of the scientific city atmosphere that reigned in 19th-century Vienna.

In the final analysis, it was in his plays that Arthur Schnitzler was most critical of medicine, as in Paracelsus (1899) where he described the European fascination for the hypnotism that was ridiculed by the Vienna School. By recounting the ca- bal mounted against the physician Paracelsus, accused of charlatanism, Schnitzler transposed into 16th-century Basel the attacks that he himself suffered in his youth when he practiced hypnosis: “[Some] slyly put about the rumor that I staged ‘shows’ at the Poliklinik, the immediate effect of which was to stop me conducting my experiments in front of a large audience, although I continued them for a while in front of reduced numbers.” Schnitzler adopted a more humoristic tone in Professor Bernhardi (1912), a play that immersed the reader-spectator in a hospital not dissimilar from the Poliklinik of Johann Schnitzler, featuring a medley of white-coated caricatures: “from the preposterously-named Hochrötznopner, a heel-clicking student capable of the basest of behavior in...
order to get ahead, to kindly Cyprian, the honest and sententious professor, via the stubborn ’60s-style liberal protestor, the unscrupulous careerist, the personification of vanity obsessed with letters after his name, and the dedicated man of science.”  

Beneath its superficial levity, the play describes the disgrace of a man reproached less for his professional failings than for his religious convictions. It was Schnitzler’s way of stigmatizing the rise of anti-Semitism in the Austro-Hungarian Empire while satirizing the medical establishment that contributed to the Empire’s fame.

The legacy of the Viennese school
Throughout the 19th century, world medicine centered on Vienna and the prestige of figures such as Rokitansky, Škoda, and Billroth. Even if Vienna was sometimes fickle and failed to recognize and justly reward some of its most strikingly innovative minds, it epitomized scientific progress and was an inspiration for artists. The name of the Vienna School remains written in gold in the history of medicine and its star never ceased to shine, even after the decline of the Habsburgs and the downfall of the Empire.

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Emoticons in marble and bronze: Messerschmidt’s intriguing “character heads”

by P. Poullalié, France

Who are these characters who laugh and weep, sing and yell, moan and gnash their teeth, who shudder and shake and wince in the eternal silence of the Belvedere in Vienna, of the Slovak National Gallery in Bratislava? Self-portraits perchance? One and the same man, his countenance frozen in myriad expressions? Or, in the spirit of the Enlightenment, a scientific study of expressions of the soul? Did the artist seek to give form to his woes, to free himself from inner demons? He plays with the principle of series, with repetition, molding a strange and somber material — metallic, yielding, elastic — into heads so true to nature that they could be mistaken for life masks. These are the creative choices of a modernist. Yet the sculptor of these baffling and unfathomable heads, Franz Xaver Messerschmidt, was born nearly three hundred years ago.


“Oh, the most violent Paradise of the furious grimace!”
Arthur Rimbaud, Parade. In: Illuminations, 1873-1875

Franz Xaver Messerschmidt was born into a family of sculptors in 1736 in Wiesentsteig, in the Swabian Alps. His uncle, Johann Baptist Straub, one of the masters of the Rococo style in Bavaria, took him on as a 10-year-old apprentice after the death of his father. Franz Xaver continued his apprenticeship under three other uncles, the Straub brothers Philipp Jakob and Johann Georg, and then Joseph with whom Messerschmidt perfected the astonishing mastery of wood sculpture which later so dazzle his fellow students in Vienna and Rome. When sixteen, Messerschmidt began training at the Academy of Fine Arts Vienna under the renowned 18th century masters Matthäus Donner and Jakob Schletterer, studied with the sculptor Balthasar Ferdinand Moll, and developed his metalworking technique using an alloy of lead and tin.

Life and works
The rector of the Academy of Fine Arts Vienna, the painter Martin van Meytens, supported Messerschmidt, who received his first commissions from 1760, after which his reputation grew. From the outset, Messerschmidt executed with great skill works remarkable in their majesty and attention to detail. This was the beginning of a rich artistic decade. Messerschmidt made imperial busts and larger-than-life statues of Empress Maria Theresa, (2 meters high) and of her husband Francis I, the Holy Roman Emperor (2.16 meters), the most remarkable statues of the age in
in 1771 he fell victim to a mysterious and to this day unelucidated mental instability. This breakdown seems to have triggered Messerschmidt’s work on the heads, to which he devoted the whole of the next decade.

Modern interpretations of Messerschmidt’s mental breakdown vary. Using historical accounts and analysis of the works, Ernst Kris, the Austrian psychoanalyst and art historian, concluded that Messerschmidt was schizophrenic. Rudolf and Margot Wittkower, the German art historians, saw him as an eccentric who was paranoid at certain times of his life.

The flow of commissions dwindled and Messerschmidt found himself isolated. During this period of alienation Messerschmidt did, however, receive a commission for a bust of Gerard van Swieten, the Dutch-Austrian physician, and another, recently discovered, of Joseph Wenzel, Prince of Liechtenstein. Yet lacking exhibitions and sales, his pecuniary situation became untenable, and he had to sell his house. On 19 May 1774, old Professor Jakob Schletterer died. Contractually, the professor’s post should have gone to Messerschmidt, but over the previous three years the word was that he “sometimes seems to lose to his mind,” and though his health had improved since the breakdown, he still manifested “some brain problems” and from time to time showed signs of a “morbid imagination.” Messerschmidt was passed over for the professorship. Two official documents dated 1774 allude to this deterioration in the sculptor’s health: a report by the academic council of the Academy of Fine Arts Vienna and a letter Prince Kaunitz sent to Maria Theresa. The empress was advised that the afflicted artist should be given a modest pension and could perhaps work for the imperial buildings, but Messerschmidt refused the pension, particularly as no commissions were attached. He resigned from the Academy, left Vienna on 8 May 1775, and went to the Bavarian village of Wiesensteig, his birthplace, to live with his mother, taking with him the first five heads. The situation though was unbearable as his mother had sold the house to her son-in-law. So Messerschmidt set up in a hut and resumed work on the heads.

This exile and solitude were short-lived because at the end of the year he moved to Munich where the Court had promised him commissions, even a position. Messerschmidt hoped to present six sculpted heads to the Prince Elector of Bavaria, to showcase his talent, but nothing came of it.
Emoticons in marble and bronze: Messerschmidt’s intriguing “character heads” – Poullalié


The Archvillain. Sculpture by Franz Xaver Messerschmidt. Österreichische Galerie im Belvedere. © akg-images/Erich Lessing.

The Beaked. Sculpture by Franz Xaver Messerschmidt. Österreichische Galerie im Belvedere. © akg-images.
After this failure, Messerschmidt left Munich in August 1777 and set up house in Pressburg (modern-day Bratislava, the capital of Slovakia), a flourishing city and the capital of the government of the Kingdom of Hungary. His younger brother Johann Adam Messerschmidt, also a sculptor, had a house and studio there and created living and working space for

Franz Xaver. Although the brothers did not see eye to eye, this arrangement lasted for five years before Franz Xaver moved into his own house, “The Hart’s Abode,” in December 1780.

Messerschmidt’s main sponsors in Pressburg were Prince Albert of Saxony, Duke of Teschen, and two counts. His reputation for oddness did not hinder the flow of commissions, and he executed the works in a neoclassical style with a very hard rendering of the face, which contrasted with the minute details of the hair and clothes. It was during this period that Messerschmidt produced most of his heads. And it was the heads that made his name. Men of letters and travelers passing through wished to meet the artist and discover his work.

Birth of a legend

The German writer Christoph Friedrich Nicolai left us an exceptional record of his visit to Messerschmidt in 1781. Full of anecdotes, his account should, however, be viewed with circumspection. Nicolai presents Messerschmidt as a “singular” man and artist, a solitary genius in the grip of attacks by evil spirits from which he could only escape by pinching himself hard under the lowest right rib. “…He observes himself, grimaces into the mirror… All the heads represent his image. I saw him work on the 61st head. He looked at himself in the mirror every thirty seconds and carefully pulled the faces needed. As works of art, these are genuine masterpieces.”

According to Nicolai, it was in Vienna (through Messmer?) that Messerschmidt entered into relations with Freemasonry, Rosicrucianism, and secret sects conversing with the spirits and claiming access to the secrets of the universe. Messerschmidt’s fascination with the esoteric theories of these secret societies is attested by his interest in the art of Ancient Egypt, his allusions to the god Thoth, the ibis-headed man of the Egyptian pantheon of deities, and a sketch of an armless Egyptian statue that he stuck on his window.

This interest in things Egyptian was not solely philosophical, but also artistic, as witnessed by his bust entitled A Seriously Injured Person, which we know of thanks to a plaster copy made in the 19th century and whose hair irresistibly suggests an Egyptian headdress.

Nicolai speaks of Messerschmidt’s belief in the apotropaic magic of the heads, of the chasing away of evil spirits, notably the “Spirit of Proportion,” which “frightened and plagued him at night” and who, he felt, was jealous of his remarkable learning, and of the fact that he had uncovered the secret of the proportions. He who, wrote Nicolai, “has always lived chastely,” suffers from “painful sensations in the lower belly and thighs” when he sculptures a part of the face that “corresponds to a certain part of the nether regions of the body.” The vital talismanic purpose of these works is attested by the fact that Messerschmidt refused to sell the heads, even though he claimed to want to make even more beautiful ones if he found a taker.

Critical fortune and modernity

Sixty-nine heads were found in the artist’s house upon his sudden death at age 47, apparently of pneumonia. Fifty-three, in wood, alabaster, wax, and lead, were preserved. Ten years later, in 1793, an exhibition at the Citizen’s Hospital in Vienna displayed 49 heads, which were seen as freakish works rep-
representing monstrosities or caricatures of human expressions. An anonymous brochure soon dubbed them “Character Heads.” Each was given an illustrative title which, naturally, bore no relation to the artist’s intentions. Messerschmidt himself called them head pieces (Kopfstücke), and saw them as a means of expressing the whole range of human expressions, which he believed numbered 64.

We have a visual record of the 49 heads thanks to Matthias Rudolph Toma (see cover), who published a lithograph, based on an earlier drawing, four years after they were first exhibited in 1835 by their owner Josef Jüttner, who showed them again in 1853. One commentator wrote: “Messerschmidt, this expert of the esthetic of the ugly, can with good reason be considered the Hogarth of sculpture.” Irremediably dispersed at an auction in 1889, the 49 heads have over the years been tracked down using Toma’s famous lithograph.

Camillo Sitte, a renowned Viennese architect, was the first who tried to collect the Character Heads, and at the 1889 auction bought a large number both privately and above all as director of the Staatsgewerbeschule (state industrial school) for an educational exhibition. It is thought that Egon Schiele discovered Messerschmidt’s works at this exhibition.

From this moment on there was a veritable rehabilitation and artistic and scientific reappraisal of Messerschmidt’s work. In particular, Emil and Berta Zuckerkandl, ardent defenders of the paintings of Gustav Klimt, did much to reunite the Character Heads. Emil Zuckerkandl was an eminent physician, professor of anatomy, and author of numerous studies on the anatomy of the head and particularly the nose. His wife, Berta, who had trained with Albert Ilg, one of the first historians to rediscover Baroque art and the author of the first serious study of Messerschmidt in 1885, throughout her life ran brilliant literary and intellectual gatherings where artists were able to discover these highly original sculptures. Around 1905-1906, some of the Character Heads were presented to the public by the playwright Richard Beer-Hofmann, who had been a member of Young Vienna (Jung Wien), a society of writers who met in Vienna’s coffeehouses in the 1890s. Against the backdrop of the movement of the Vienna Secession and the Vienna of Freud, the Character Heads intrigued, fascinated, and inspired painters, writers, and doctors.

Others found a more mundane use for the heads. Right up until the 1960s, copies cast in molds taken from originals served as targets on shooting ranges or were used to compose freakish and parodic scenes at the Prater, an amusement park in Vienna. Still more could be seen in a hat shop window, and three decorated a wine bar in the Hungarian town of Esztergom. Once aroused, the elite’s interest in the Character Heads never waned. Picasso owned a set of images of the heads, and Ludwig Wittgenstein kept a copy of The Simpleton on his desk.

From shooting ranges at the Prater, Messerschmidt returned to the world of the museum, through exhibitions of his Character Heads, but also by inspiring major contemporary artists like the Austrian Arnulf Rainer, the British sculptor Tony Cragg, the British painter Tony Bevan, and the French artist Bernard Crespin and his series of self-portraits. Messerschmidt is indissociable from modernity in the minds of museum curators. The Louvre in Paris presented the Character Heads with sculptures by Tony Cragg in 2011, and the J. Paul Getty Museum in Los Angeles in 2012 staged an exhibition entitled “Messerschmidt and Modernity,” which presented sculptures by Messerschmidt and works by contemporary artists who draw inspiration from his work.
Emoticons in marble and bronze: Messerschmidt’s intriguing “character heads” – Poullalié

**Self-Portrait after Messerschmidt.** Tony Bevan, 2009, acrylic and charcoal on canvas, 99×80 cm. © Tony Bevan/Galerie Vidal-Saint Phalle. With kind permission.

**Der Strichstricker.** Arnulf Rainer, 1970s (After Messerschmidt, “Der Heftige Geruch” – “The Strong Smell”), ca 60.7×47.5 cm, lead pencil on photo. © Arnulf Rainer. With kind permission.

**Bad Guys.** Tony Cragg, 2005, bronze, 120×100×110 cm, photographer Lothar Schnepf. © Tony Cragg. With kind permission.

**Ricordo #10.** Bernard Crespin, 2010/2011. Pigment print on paper (unique proof), 102.5×82.5 cm. © Bernard Crespin. With kind permission.
The legend under the scrutiny of stylistic interpretation

Of 49 heads catalogued in 1793, a total of 38 originals are accounted for today, plus six variants that were not part of the set of 49. These heads sustain the romantic myth of the mad, solitary genius, but a stylistic analysis puts these heads squarely in the esthetic and philosophical context of their time. This analysis reveals a virtuoso artist, recognized, sought after throughout Eastern Europe, scion of a family of famous sculptors, welcomed in the studios of the greatest artists of his time. Although Messnerschmidt trained in the Rococo tradition of sculpture, he is the harbinger of the movement of art toward the classicism of antiquity. Sickly is it true, aggressive and uncouth with those around him, Messerschmidt was nonetheless aware of the philosophical and artistic movements of his time: Enlightenment ideas, esoteric knowledge, the magnetism of Franz Anton Mesmer, pathognomonic analysis, the Swiss Johann Kaspar Lavater’s physiognomy, the somnambulism induced by A. M. J. Chastenet de Puységur.

Messerschmidt’s stylistic evolution can be detached from the psychological crisis of 1771, insofar as his art presents perceptible changes from the pivotal period between 1767 and 1769 when he received the commission for the bust of van Swieten. This stylistic and esthetic progression was consolidated with the realization circa 1780 of the spectacular lead-tin cast of the head known as Capuchin.

From the outset, then, Messerschmidt proved innovative and distanced himself from the official Rococo style, a tendency that quickly became marked in his portraiture. Messerschmidt abandoned the bust, which was a pretext for spectacular and dramatic effects of draped clothing or for decorative and symbolic elements like medals, jewelry, symbols of the subject’s power and status. Instead, he used a frontal representation of a bare head, in contrast to the official portraits of that time in which the subjects were bewigged.

Messerschmidt refused to idealize or to embellish portraits and made them as realistic as possible, seeking to translate their intemporal truth, in contrast to the Baroque, which sought to translate movement and the ephemeral.

Messerschmidt was the only artist to propose neoclassical portraits uncompromised by the triumphal Baroque style of the era. This stylistic evolution has no equivalent among Messerschmidt’s peers. He drew inspiration from the frontal and realistic portraits of the end of the Roman Republic that he discovered during his stay in Rome, and from his knowledge of the sculpture and art of Ancient Egypt. This quest for the ideal does not break completely with a sensual rendering, which preserves something of the Baroque spirit. Remarkably for the time, the Character Heads were not commissioned and none was sold during the artist’s lifetime, despite attractive financial offers. Messerschmidt, at Pressburg, made extremely costly marble busts for wealthy clients, not to mention the sale of alabaster medallions which he entrusted to his servant and which gave the artist a certain wherewithal and allowed him to pursue his work on the heads. This is an extremely modern approach.

The legend rides the winds of change

One should not forget the philosophical and esoteric world in which artists moved or Mesmer’s theories and treatments, which were familiar to Messerschmidt. Some critics interpret the gag, the rope around the forehead or neck of certain heads as the magnetics or accessories that Mesmer attached to his edge of the sculpture and art of Ancient Egypt. This quest for the ideal does not break completely with a sensual rendering, which preserves something of the Baroque spirit.
patients to stimulate the flow of magnetic fluid. Nicolai reports another, more tormented, explanation given by Messerschmidt himself: “Man must completely draw in the red of his lips, because no animal shows it.” The artist was convinced that animals were superior to humans in the perception of a good many things, notably the spirits, “the absence of obvious lips in animals” being the explanation, whence the effacement of lips on his heads.

**The mystery remains: the problems of series**

Messerschmidt maintained, once more according to Nicolai, that there are 64 different expressions or “grimaces” that express all the proportions of the head and, by extension, of the human body. The series of heads was intended to review and fix forever these 64 versions of the proportions. In truth, careful analysis of the heads shows that Messerschmidt used his own mirrored expressions to compose the heads, but also selected items already sculpted. This is not snapshot mimicry of expressions the virtuoso artist fixed in alabaster or in lead—fully an analysis of the heads shows that Messerschmidt used his press all the proportions of the head and, by extension, of the body. Each head, which is therefore in no way naturalistic.

The paradox of this work lies in its principle: the series. In appearance, the rendering is hyperrealistic. The face contorts because the body is pinched. The artist models each bulging muscle, each furrow induced by the contortion of features. But this rendition is not unique (there are variations of some heads) and is part of a repetitive, serial approach which necessitates the abandonment of naturalistic or realistic interpretation for a more formal and esthetic probing. The series annihilates veristic representation and propels us toward abstract questioning.

Moreover, the strange illusionism of these heads is not devoid of anatomical implausibilities. So the Character Heads are neither naturalistic self-portraits (some heads have features that differ completely from those of the rest of the series) nor a scientific attempt to describe the outward display of the soul’s inner workings, manifestations which would anyway be hard to pin down (from laughing to weeping, from pain to pleasure).

**The importance of, not to say obsession with, the mouth, which is reminiscent of that of the painter Francis Bacon, leads to spectacular and complete misshaping of the whole head in the two heads called *The Beaked*, in which the face ends in a birdlike beak. These two heads terrorized the artist. Nicolai relates that: “[The spirit] pinched him again and again until the faces saw daylight. He [Messerschmidt] thought ‘I’ll get the better of you yet’, but admitted that he had almost died in the attempt.” However we interpret the series, these heads are not the artist’s inner, intangible self portrayed through a glass, darkly.

**Everlasting modernity**

Historical facts, their interpretation, dismantle the fascinating legend of Messerschmidt as the “damned” artist, the mad genius who withdrew to Pressburg, sculpting fearfully in a desperate fight against his inner demons and the Spirit of Proportion. What remain are his heads, larger than life, so precisely and convincingly fashioned that their creator has earned an everlasting presence through his works. The force of this work is such that its mystery is preserved and lasting and all musings and interpretations are permitted…. It is perhaps just this which explains the beauty, the vitality, the modernity of Messerschmidt’s Character Heads.

**Further reading:**

Légende et vérité inextricablement mêlées, sculptures authentiques et copies indifféremment exposées, l’œuvre de Franz Xaver Messerschmidt (1736-1783), depuis deux siècles qu’elle a été redécouverte et réhabilitée, fait toujours l’objet d’interrogations et d’interprétations contradictoires … Artiste réputé à la cour des Habsbourg, sculpteur des célèbres « têtes d’expression », l’œuvre de Messerschmidt, après avoir été méprisée et raillée dans les baraques foraines du Prater, a connu un regain d’intérêt dans la Vienne fin de siècle qui ne s’est plus jamais démenti. Aujourd’hui encore, comme si Messerschmidt était toujours vivant parmi nous, les plus grands musées du monde se battent pour acquérir les dernières têtes en mains privées et les exposent le plus souvent en compagnie des œuvres que Messerschmidt a inspirées aux artistes contemporains les plus réputés. Etonnant destin que celui d’un sculpteur que la légende a voulu faire passer pour un fou solitaire et qui ne cesse d’intriguer et de fasciner grand public, critiques d’art, artistes et médecins. Au-delà d’une vie dont les péripéties sont difficiles à expliquer, au-delà d’une interprétation historique ou d’une interprétation psychiatrique et psychanalytique, la découverte des « têtes de caractère » de Messerschmidt provoque, par-delà le temps, un véritable choc et une étrange fascination.
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