Karger Gazette

No. 69
Published April 2007

Mind & Body

Mind & Body

EDITORIAL

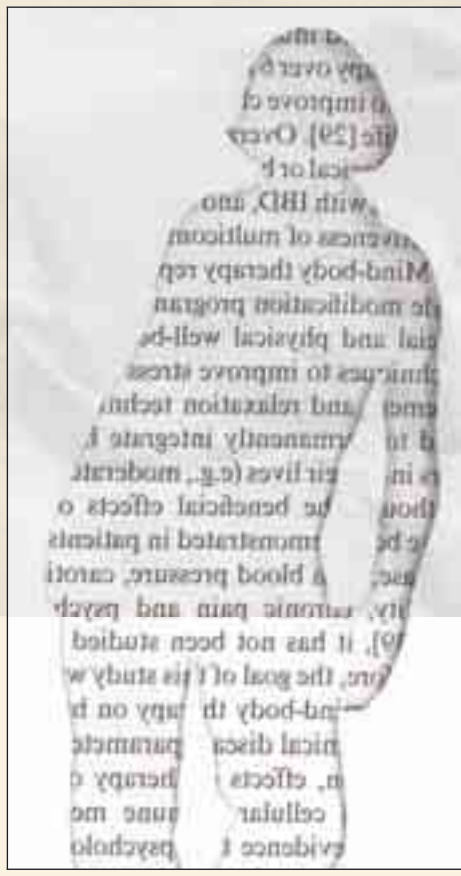
Rapidly rising costs in health care, an increasing focus on preventive medicine, the risks, uncertainties and stresses associated with an ever-accelerating globalized world – these are just some of the features of contemporary Western society that may account for the growing attention being paid by both medical professionals and the general public to the interactions between the mind and the body. To how our psychological life impacts, negatively and positively, on our physical health. And vice versa.

There are many manifestations of this interest, ranging from countless alternative therapies which some consider esoteric – if not downright 21st-century quackery – to the hard science of the neurobiology laboratory. This issue of the Gazette cannot address all aspects of the topic, and its focus is largely a medical one. We open with a historical account of the mind-body relationship in Western philosophy and science, tracing in particular the changing fortunes in concepts of the mind-body partnership from the 17th to the early 20th century. This is followed by a review of the status of psychosomatics today, with a plea for the integration of this field into general medicine. The issue closes with two "case studies" – one on the placebo effect and one on the consequences of trauma – both of which provide fascinating insight from different perspectives on the interconnections and mutual influences of our psyches and somas.

With its biomedical emphasis, the aim of this Gazette is to offer readers some sense of what is currently known about the physiology, chemistry and neurobiology of mind-body interactions, but we hope it will also stimulate reflection on the challenges still posed to this field.

Perhaps one of these challenges remains a conceptual, even a linguistic one. By continuing to refer to the mind and body as two entities – a problem somewhat overcome in the terms *psychosomatics* and *biopsychology* – the danger remains of reducing the mind's processes and activities to purely bodily ones, because it is scientifically and methodologically feasible, for example, to measure and quantify them in the form of electrical signals or chemical reactions. In this pursuit, nonobjectifiable properties of our mental worlds, of our memories and imagination, may be neglected, ignored or, at least, not fully accounted for. As research continues into this intriguing, and yet far from resolved relationship, its interdisciplinarity may need to expand beyond the compass of medical scientists, psychologists and philosophers to embrace the work and insights of e.g. visual artists, musicians and writers. Such a reintegration of "the two cultures," in C.P. Snow's phrase, may ultimately yield some of the most productive advances in both our understanding of ourselves, and in medical care.

ab



Partners and Strangers: The Mind-Body Relationship in History

Lilian Furst

Chapel Hill, N.C.

The question of the mind-body relationship has intrigued — and bedeviled —philosophers, theologians and psychologists, as well as medical practitioners, throughout the ages. Even today, at the opening of the 21st century, despite the momentous advances made by medicine, it still defies complete understanding of its multiple manifestations and, above all, of its precise mechanisms.

Holistic beginnings

The history of the mind-body link is especially fascinating for the swings of the pendulum it has undergone in response to – and as an expression of – shifting beliefs and paradigms. "Until the mid-19th century . . . all medicine was necessarily and ubiquitously 'psychosomatic'," the eminent medical historian Charles Rosenberg has asserted in his incisive article "Body and mind in nineteenth-century medicine" [1]. Why "necessarily and ubiquitously"? The necessity stemmed partly from the absence of knowledge about the workings of either the mind or body so that physicians had no alternative but to resort to the speculative theories current at their time. From the days of Galen, who was born in A.D. 130, the ubiquitous theory was that of the four "humors" which corresponded to the four elements: earth, air, water and fire. In the human being, these became manifest as cold, dry, moist or hot temperaments. Good health resulted from an equal balance of the four; illness, on the other hand, arose when one or the other got the upper hand. The therapeutic corrective was to apply the opposite: hot to cold, dry to moist, and so forth. In practice the most crucial facet of this system was its total reliance on an approach that was at once holistic and fundamentally individual. Since every patient had his or her particular temperament, the physician's primary task was to identify the prevalent humor in order to select the appropriate counteragent to the illness. External factors such as season, climate and age also played an important role in both diagnosis and remedy. One direct consequence of this overarching emphasis on the patient's individuality was the need for the physician to have an intimate, extended familiarity with the sick person. The greater and deeper the physician's knowledge of his patient, the greater the likelihood that he would be able to prescribe the optimum mode of treatment. The crux of this system was the conviction that illness and, therefore, treatment were *patient specific and invariably individual.* The aim of medicine, to restore homeostasis, rested squarely on the unquestioned supposition of the reciprocity of mind and body.

Thomas Sydenham

This essential interdependence of soma and psyche remained the foundation of medical theory and practice certainly into the first third of the 19th century and indeed later, particularly in more remote regions removed from the orbit of innovative advances. This is not to minimize the significant progress made in the 16th to 18th centuries. To cite just some of the leading discoveries: Andreas Vesalius (1514–64) mapped human anatomy; William Harvey (1578–1657) traced the circulation of the blood; Giovanni Morgagni (1682–1771) made the first attempts to relate clinical findings to the results of autopsies. But these early medical advances were, except for the work of Morgagni, concerned with the functioning of the body in good health and did not prejudice the continuing acceptance of the close connection between mind and body, based on evidence accumulated from the observation of living patients.

On the contrary, expressions of belief in the unity of mind and body crop up frequently throughout the 17th to the mid-19th centuries. For example, Thomas Sydenham (1624–89), the preeminent British physician of his time, declared repeatedly and unequivocally that psychological factors were involved in pathogenesis. A series of monographs appeared in the 18th century that sought to offer a systematic presentation of contemporary thought on the influence of the mind upon the body. William Corp's Essay on the *Changes Produced in the Body by the Operations of the Mind* (1791) and William Falconer's *Dissertation on the Influence of the Passions upon the Disorders of the Body* (1788) discuss both the potentially deleterious and the beneficial effects of the patient's mental status on his or her physical condition. It was universally recognized that thoughts and feelings, such as grief, anger, anxiety and fear on the negative side, or hope and joy on the positive, could have a mediated impact on the patient's bodily disarray or well-being.

Outstanding among these treatises are two essays published under the title *De regimine mentis* (1747 and 1763) by Jerome Gaub (1705–80), a professor of medicine at Leiden, whose work was widely known and heeded in the 18th century [2]. In considering the issue of the relation of body to mind in human ailments, Gaub presented clearly, forcefully and often elegantly a summary of current opinion. His opening section, "The harmony of mind and body" situates him centrally in the tradition of humoral medicine. The vital interplay of mind and body is a recurrent theme of all his essays, as their titles indicate: "Mind and body interaction in the normal state," "Mind and body interaction in states of imbalance," "Corporeal effects of expressed and suppressed emotions compared." Gaub's advocacy of the mind-body dynamic is impressive; he ends by stating unambiguously that it is "quite plain that the causes and occasions of a great many of the afflictions of the body arise in the mind, as it were from a fountainhead."

Franz Anton Mesmer

The interdependence of mind and body was also acclaimed in the late 18th and early 19th centuries by powerful voices within the medical community. Pierre Jean George Cabanis (1757–1808) issued a stern warning against the medical man who had not learnt to read the human heart as well as to recognize the febrile state. A parallel view was expressed by the distinguished American physician Benjamin Rush (1745–1813) who admonished his colleagues always to see the patient as a single, indivisible being.

The ubiquity and persistence of such beliefs is also reflected in 19th-century fiction in which a good many characters are portrayed as suffering from bodily afflictions that seem to stem from some kind of psychological stress. Lisa, the young girl in Dostoevsky's *Brothers Karamazov* (1880), is confined to a wheelchair with her legs paralyzed at the beginning of the novel, but is suddenly and spontaneously cured once she escapes her scheming mother's nefarious clutches. No less than four of the main figures in Charlotte Brontë's *Shirley* (1849) display states that devolve from a fusion of psyche and soma. Likewise, Balzac's novel *Le Cousin Pons* (1847) traces the decline and death of a musician after he comes to realize the viciousness of the very people he had most trusted as his friends. But by far the most widespread malady of the time was the brain fever that invariably followed a severe shock of some type [3, 4]. The most famous cases are those of Emma in Flaubert's *Madame Bovary* (1857) who falls into a nearly fatal state when her lover, Rodolphe, jilts her, and Catherine Linton in Emily Brontë's *Wuthering Heights* (1847) who succumbs to the fever. Similar instances abound: Pip in Dickens's *Great Expectations* (1860–61), Roghozin in Dostoevsky's *The Idiot* (1869) and a number of Sherlock Holmes's protagonists when they find themselves boxed into untenable situations. The prostration, loss of memory and confusion characteristic of these so-called brain fevers seem to point to a form of post-traumatic stress disorder rather than a neurological disease.

Marie-François-Xavier Bichat

The climax – and simultaneously the *reductio ad absurdum* – of the doctrine (for such it had become) of the mind-body relationship comes in the antics of Franz Anton Mesmer (1734–1815). It is hard to know how to designate him for he was considered a veritable magician by some and no more than a mere charlatan by others. After completing his medical studies in Vienna in 1766 and being banished for having caused scandal, he moved to Paris where he conducted a sort of medical practice in the form of a salon. On the postulate of an imponderable fluid that permeates the entire universe, infusing both mind and matter, he used magnets to redistribute this fluid within the patient so as to restore equilibrium in a manner reminiscent of the homeostasis sought by humoral medicine. Intuitively aware of the psychological dimensions of many illnesses, Mesmer also induced spellbinding trances and had recourse to forceful interpersonal suggestion and rites of exorcism to re-establish a healing link between mind and body. Mesmer's practices are remarkable for their mingling of quackery, showmanship, and an instinctive grasp of the interplay of mind and body.

The technological hiatus

What then happened, largely in the first half of the 19th century, to reverse this trend, to elevate the body to the prime site in the discipline of medicine while relegating the mind to a subservient position? Put in a nutshell, the decisive turn was consequent to the invention of a se-

ries of instruments that enabled doctors to attain a better understanding of the body's functioning literally through in-sight beneath its surface. The first and perhaps most important of these instruments was the stethoscope devised in 1816 by the Breton René-Théophile-Hyacinthe Laënnec (1781–1826). Instead of having to depend on patients' subjective accounts of their symptoms, the physician could now, by means of the stethoscope, rely on his own interpretation of the sounds he himself heard, differentiating, for example, through his experience with abnormalities of the lungs, between pneumonia, pleurisy and tuberculosis. The practice of medicine could thus become more objective and more scientific. Other instruments that came into use in the course of the 19th century, such as the laryngoscope, the bronchoscope, the ophthalmoscope, the endoscope and the urethra-cystic speculum, served the same purpose as the stethoscope in achieving objective diagnoses by penetrating beneath the body's exterior. The culmination of this development was the introduction of X-rays by Wilhelm Konrad Röntgen (1845–1923) in 1895.

The entire conceptualization of medicine was radically transformed not only by the application of this battery of instruments but also by the combination of their findings with those of the pathological anatomy initiated at the very opening of the century by Marie-François-Xavier Bichat (1771–1802). By conducting hundreds of autopsies in winter (the smell was too bad in summer), Bichat saw distinctive lesions in particular organs and realized that the source of disease was a *local* abnormality. This discovery instigated one of the most fundamental revolutions in the history of medicine: the turn away from the patient specificity of earlier times to the *disease specificity* of modern medicine. Instead of envisaging the whole body and mind as out of balance, in the wake of Bichat, doctors sought to pinpoint the singular lesion at the core of the patient's symptoms. What is more, the categoric ravages that Bichat found in cadavers as the telltale signs of particular diseases could be directly related to the sounds emitted by the living patient and picked up on the stethoscope. The connection between what was audible in the patient and what was visible in the cadaver allowed doctors to deduce a firmly grounded taxonomy. The conjunction between the damage uncovered by pathological anatomy and the findings produced by the new instruments accomplished the transition to a scientifically based practice rooted in pragmatically established facts. Some 50 years after Bichat, Rudolf Virchow (1821–1902) in his famous work *Cellular Pathology* (1858), engaged in the comparative analysis of healthy and diseased tissues.

Daniel Hack Tuke

The scientific approach was also furthered by the introduction in the 1860s and 1870s of the numerical method sponsored by the French researcher Pierre-Charles-Alexandre Louis (1787–1872) who championed statistics on the grounds that truth resided in objective facts. Meanwhile, improvements in the power and accuracy of microscopes paved the way for the extraordinary advances in bacteriology made by the French chemist Louis Pasteur (1822–95) and the German country doctor Robert Koch (1843–1910), who succeeded in identifying a diverse spectrum of microorganisms and isolating each of them as the cause of a particular infection.

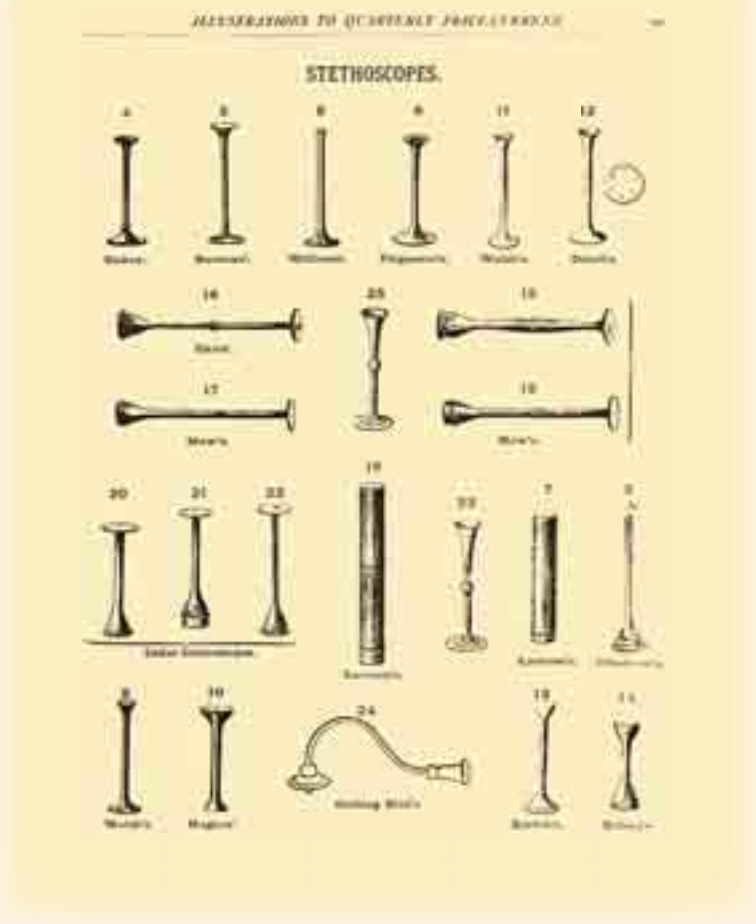
This spectacular progress in the understanding of the body made during the course of the 19th century had as its unfortunate corollary a neglect of the mind. Psychiatry had already been held in low esteem in the 18th century when its practitioners were called "mad doctors" because they functioned mainly as custodians of the insane and the mentally disturbed. With the increasing emphasis on the body in the 19th century, the mind was largely pushed aside. The disparity between the respective knowledge of the body and the mind had become glaring by the last third of the century. The problem was compounded by the displacement of psychiatry by the new discipline of neurology, whose focus was on the study of the brain, i.e. the physical aspects of mental activity. The German Wilhelm Griesinger (1817–68) was the major proponent of neuropsychiatry, which argued that mental disorders were actually diseases of the brain.

Jean-Martin Charcot

Efforts were made to clothe all illness in somatic garb on the supposition of some as yet undiscovered lesion. This approach was encouraged by the recognition that delirium tremens stemmed from the abuse of alcohol and that the general paralysis of the insane was a consequence of syphilitic infection. Lesions won out over feelings, the body over the mind. One curious instance of this tendency was the affliction popular in the later 19th century, neurasthenia, which was literally invented by the American physician George M. Beard (1839–83), who launched the syndrome in an article in the Boston *Medical and Surgical Journal* of 1869. Neurasthenia as a weakness of the nerve centers, often the result of overwork, was essentially a physical malady without any of the stigma attached to mental illness. So Margaret Cleaves, a New York doctor, was assured in the later 1880s that she had "sprained her brain" [5, 6].

But the mind and the caprices of the imagination could not be so readily banished once and for all, even though they remained an enigma. A curious, neglected work, *Illustrations of the Influence of the Mind upon the Body in States of Health and Disease, Designed to Elucidate the Action of the Imagination* was published in 1872 by Daniel Hack Tuke (1827–95), a physician who had practiced for many years before having to take extended rest on account of tuberculosis. Tuke reflects on the many puzzling cases he had experienced in which feelings such as joy, fear, anxiety or disappointed ambition had precipitated physical reactions. He recalls a 20-year-old woman who lost the power of speech after seeing a mouse run under a table, another woman who was hospitalized in a catatonic state for 3 weeks after seeing one of her children scald herself, an 8-year-old girl who, on being separated from her mother, exhibited delirium, headaches and an inability to stand, resistant to every form of treatment, yet who recovered as soon as she was reunited with her mother. Tuke is perplexed by what he calls these "psycho-physical phenomena." While recognizing and illustrating the involvement of the imagination, he is quite at a loss to explain it. He therefore falls back lamely on the standard physicalist language of his time by reference to spasms, contractures, vaso-motor nerves and cerebral ischemia. Tuke senses that other factors are at work too, but he is ultimately unable to "elucidate" them satisfactorily [7].

The word "imagination" occurs too, albeit only very rarely and grudgingly, in the work of the brilliant French neurologist Jean-Martin Charcot (1825–93). As head of the enormous Salpêtrière hospital for women in Paris, he presided over what he described as a museum of pathologies affecting all parts of the nervous system. The most favored diagnosis was that of hysteria, which could comprise paralyses, contractures, muteness, deafness, blindness, fixities and so on. In keeping with the trends of his time, Charcot sought by cerebral localization to find the lesions underlying these variegated symptoms. He applied all manner of physical remedies: compression, friction, metallotherapy, massage and electrotherapy. However, somatic medicine could not decipher these disorders, let alone remove them. So, faced with some surprising cures, Charcot came to conclude that "Chez ces femmes la guérison était survenue tout d'un coup, au milieu de circonstances bien propres à émouvoir l'imagination" ["In these women the cure had occurred all of a sudden under circumstances very apt to affect the imagination"] [8].



Nineteenth-century stethoscopes (catalog illustration, 1869; National Library of Medicine, Bethesda, Md.)

Nonetheless, despite this concession, Charcot insisted on defining psychology in relation to nervous diseases as the rational physiology of the cerebral cortex – an opaque statement that bears out the 19th century's predilection for subjugating the psychological to the physiological.

Sigmund Freud

Nor was hysteria the only phenomenon to pose a challenge to the prevailing norms of somatic medicine. The problem of pain without a visible or diagnosable physical injury became a discomforting medical and legal issue with the increase in railroad travel and accidents. Numerous hypotheses were put forward in attempts to account for phenomena that contravened the medical tenets of the day. A pamphlet on "The Influence of Railway Travelling on Public Health," published in the *Lancet* in 1862, argued that passengers actually sustained a series of small, rapid concussions from the machine's vibrations that could be transmitted from one part of the body to another. This theory was invoked to explain such aftereffects as insomnia or headaches. Since financial compensation and lawsuits were often at stake, discussion of these cases was intense though inconclusive [9].

Freud

This is the atmosphere of doubt and skepticism in which Sigmund Freud (1856–1939) published his *Studien über Hysterie* (*Studies on Hysteria*) in 1895. Freud had not only undergone a conventional medical training in Vienna, he had also been a pupil of Charcot's in Paris in preparation for his intended career as a neurologist. He was clearly hesitant about shifting into psychiatry, a field still considered with suspicion as highly speculative terrain in contrast to the certainties thought to buttress somatic medicine. He insisted on pointing out that he was fully conversant with electrotherapy and the other methods of treatment customary at the time. By opting to develop his own approach in what came to be known as "the talking cure," he was taking a considerable professional risk. His unease at this juncture reveals how profoundly he had been shaped by the scientific imperative in the practice of medicine and how wary he was of departing from the prescribed rigorous set of procedures. But his clinical experiences with his patients soon convinced him that the standard physical

treatments of his day – rest, massage, electrotherapy, hydrotherapy – were ineffective for "nervous" disorders.

Studies on Hysteria affords a fascinating glimpse of the genesis of "the talking cure." For his first patient, Emmy von N., a wealthy German widow with two daughters, Freud began by applying all the accepted treatments. While massaging her daily, he noticed how she started to talk as if casually, producing each time the memories and associations that had occurred to her since their previous meeting. As soon as Freud realized that her talk was by no means as unintentional as it seemed, he hit upon the cornerstone of psychoanalysis, the principle of free association.

With the other patients chronicled in the *Studies*, Freud turned his back on the normative physical therapies. Instead he began to experiment with ways to address the mind; for a while he tried hypnosis, a method used by Charcot and his followers, but he found it unsatisfactory. With one patient, Elisabeth von R., he placed his hands on her head in order to stimulate memories. However, this too he soon abandoned, eschewing all bodily contact so as to concentrate on intensive listening to his patients' free associations as they lay in a relaxed position on a couch. He himself remained seated behind them, out of sight, interjecting only occasional comments. In this situation the physical, including the doctor's gaze, is eliminated as far as possible, thereby directing the fullest attention onto the mind.

If free association represents the means Freud more or less stumbled on as the tool to open up the hidden recesses of the mind, his most momentous contribution by far to the history of the mind-body relationship was his understanding of the existence of the unconscious and its role in human behavior. The concept of the unconscious, so conspicuously absent from Tuke, was an immense advance on the vague idea of the "imagination." In his analysands' apparently spontaneous talk, Freud came to recognize the manifestations of unconscious levels of the mind that surfaced in such formerly unexplained phenomena as forgetting, slips of the tongue and expressions of psychic distress translated into bodily symptoms (conversion). Freud drew by preference on images from the realm of archaeology, conceiving the mind as structured into three intercommunicating layers, the id, the ego, and the superego, all of which play a part in determining our actions. The mind is therefore perceived as organized like a site to be excavated.

Freud renewed the mind-body relationship by delineating the processes whereby emotions can unwittingly affect the body. His revolutionary insights laid the foundations for what George Engel denoted as the "biopsychosocial model," in a series of articles published from the late 1970s onward [10]. This concept has gained wide acceptance in everyday life as we acknowledge that a headache may be triggered by annoyance, that anxiety may result in insomnia, or that a student facing a big exam may wake up with stomach pains. In a certain sense, then, the pendulum has swung back, and though our methodologies and instruments are broader in scope and infinitely more complex than those available to the earliest physicians, a wound in western perception of the human being, and particularly the sick individual, has healed. In theory, at least, the hyphen has been restored to the mind-body relationship, the psychological reintegrated with the physical. In medical practice, application of the biopsychosocial model is likely to be neither transparent nor simple, but the dialogue between mind and body is one to which even the most technologically advanced medicine must pay heed.

Acknowledgements

I would like to record my gratitude to C.F. Irons, III, MD, for so kindly reading and providing feedback on this piece; and thanks also to Dr. Anabel Aliaga-Buchenau for help with e-mail and other practical matters.

About the author

Lilian R. Furst is Marcel Bataillon Professor of Comparative Literature Emerita at the University of North Carolina at Chapel Hill. Born in Vienna and educated in England, France and Switzerland, she was awarded her PhD by Cambridge University. She has lived in the United States since 1971 and taught at various institutions, including Harvard, Stanford, Dartmouth and the College of William and Mary, before she joined the UNC-Chapel Hill faculty in 1986. Professor Furst has published widely on romanticism, realism and naturalism. Her current research interests are in the field of literature and medicine, and post-Holocaust writing. This article draws on a chapter in her book *Idioms of Distress: Psychosomatic Disorders in Medical and Imaginative Literature* (State University of New York Press, 2003).

References

1 Rosenberg CE: Body and mind in nineteenth-century medicine. In: Epidemics and Other Studies in the History of Medicine. New York, Cambridge University Press, 1992, p. 77.
2 Rather LJ: Mind and Body in Eighteenth-Century Medicine: A Study Based on Jerome Gaub's "De regimine mentis". Berkeley, University of California Press, 1965.
3 Schiller F: A case of brain fever. Clio Medica 1974;9:181–192.
4 Peterson AC: Brain fever in nineteenth-century literature: fact and fiction. Victorian Studies 1976;19:445–464.
5 Cleaves M: Autobiography of a Neurasthene. Boston, Graham Press, 1910.
6 Furst LR: "You have sprained your brain": Margaret Cleaves's autobiography of a neurasthene. Nineteenth-Century Prose 1998;25:140–153.
7 Furst LR: Daniel Hack Tuke walking a tightrope. Nineteenth-Century Prose 2000;27:60–74.
8 Charcot JM: L'hystére (Trillat E, ed). Toulouse, 1971, p. 70.
9 Schivelbusch W: Geschichte der Eisenbahn. Munich, Hanser, 1978 [translated by Anselm Hollo: The Railway Journey: Trains and Travel in the Nineteenth Century. New York, Urizen, 1979].
10 Engel G: The need for a new medical model: a challenge for biomedicine. Science 1977;196:129–136.

The Emerging Role of Psychosomatic Medicine in Today's Medical Care

Giovanni A. Fava

University of Bologna and State University of New York at Buffalo

Modern psychosomatic medicine developed in the first half of the past century, even though the concept was introduced by Johann Christian Heinroth in 1818. It resulted from the confluence of two concepts with, as Lilian Furst has shown in the preceding article, an ancient tradition in Western thinking and medicine: the psychogenesis of disease and holism. The idea of psychogenesis characterized the first phase of the development of psychosomatic medicine (1930–1960), and resulted in the concept of "psychosomatic disease," i.e. a physical illness, such as peptic ulcer, believed to be caused by psychological factors. Despite early criticism, the psychogenic postulate exerted considerable influence in view of its explanatory power, particularly in a field then dominated by psychoanalytic investigators. George Engel, Zbigniew Lipowski and David Kissen deserve credit for laying out, in the 1960s, the ground for the current psychosomatic view of disease.

Engel developed a multifactorial model of illness, subsumed under the rubric of "biopsychosocial" [1]. In this model, illness is viewed as resulting from the interaction of mechanisms at the cellular, tissue, organismic, interpersonal and environmental levels. Accordingly, the study of every disease must take into account the individual, his or her body, and the surrounding environment as essential components of a total system. The various social factors involved may range from socioeconomic status (e.g. poverty, nutritional deprivation, loss of social support) to toxic environmental exposure, to give a truly ecological perspective. Psychosocial factors may operate to facilitate, sustain or modify the course of a disease, even though their relative weight may vary from illness to illness, from one individual to another and even between two different episodes of the same illness in the same individual. Susceptibility to disease may be influenced by activation of a variety of central nervous system pathways. The aim of such contemporary disciplines as psychoneuroendocrinology and psychoimmunology, which have evolved out of biopsychosocial research, is to unravel the complex balance and interaction between emotions and disease.

Lipowski provided an invaluable contribution by setting the scope, mission and methods of psychosomatic medicine [2]. He criticized the obsolete notion of psychogenesis, since it was incompatible with the doctrine of multicausality, which constitutes a core postulate of current psychosomatic medicine.

Kissen provided a better specification of the term "psychosomatic": "It would appear possible for an illness generally thought of as being 'psychosomatic' to be 'non-psychosomatic' in certain individuals. Likewise an illness not generally thought as 'psychosomatic' may be psychosomatic in some individuals" [3]. He thus clarified that the relative weight of psychosocial factors may vary among individuals with the same illness and underscored the basic conceptual flaw of considering diseases as homogeneous entities. Instead of asking "Which psychological factors give rise to which illnesses?" Kissen suggested we should ask "Who are the patients within a given illness population for whom psychosocial variables are of primary significance?"

Psychosomatic research has generated an impressive body of knowledge, with contributions published in all the major medical journals as well as those specifically dedicated to the field such as *Psychosomatic Medicine*, *Psychosomatics*, *Psychotherapy and Psychosomatics* and the *Journal of Psychosomatic Research*. As a result, psychosomatic medicine may now be defined as a comprehensive, interdisciplinary framework for: (1) the assessment of psychosocial factors affecting individual vulnerability, course and outcome of any type of disease; (2) the holistic consideration of patient care in clinical practice and (3) the specialist interventions to integrate psychological therapies in the prevention and treatment of medical disease and subsequent rehabilitation [4].

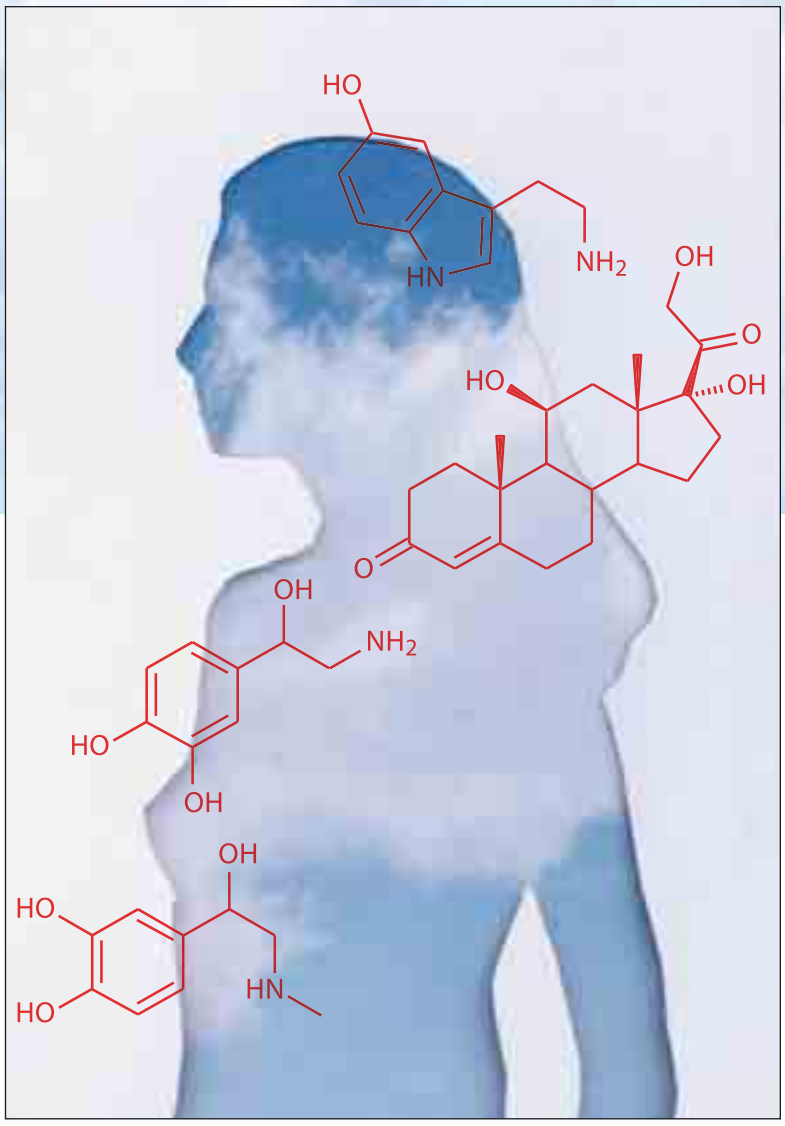
Psychosomatic medicine has recently become a subspecialty recognized by the American Board of Medical Specialties. It is, by definition, multidisciplinary, is not confined to psychiatry and should concern all physicians.

The assessment of psychosocial factors affecting individual vulnerability

A number of factors modulate individual vulnerability to disease, among which early life events have been the subject of many studies. Using animal models, events such as premature separation from the mother have consistently resulted in the development of physiological vulnerability, such as increased hypothalamic-pituitary-adrenal (HPA) axis activation and prolactin secretion. In humans, such changes may render individuals more vulnerable to the effects of stress later in life.

That meaningful events and situations in a person's life may be followed by ill health has been a common clinical observation. The introduction of structured methods of data collection and control groups has substantiated the link between life events and a number of medical disorders, encompassing endocrine, cardiovascular, respiratory, gastrointestinal, autoimmune, skin and neoplastic disease. Within a multifactorial frame of reference, stressful life events may affect the regulatory mechanisms of neuroendocrine-immune functions in a number of ways.

It is not only dramatic life changes, like bereavement or job loss, that are a source of psychological stress. Subtle and long-term life situations should not be too readily dismissed as minor and negligible, since chronic, daily life stresses may be appraised by an individual as taxing or exceeding his or her coping skills. McEwen and Stellar [5] formulated a relationship between stress and the processes leading to disease based on the concept of allostasis, the ability of an or-



ganism to achieve stability through change. Through allostasis, the autonomic nervous system, the HPA axis and the cardiovascular, metabolic and immune systems protect the body by responding to internal and external stress. An allostatic load is derived from chronic exposure to fluctuating or heightened neural or neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful. Their model emphasizes the hidden cost of chronic stress on the body over long periods of time, the concomitant changes then acting as predisposing factors for disease. Biological measures of allostatic load, such as glycosylated proteins, coagulation/fibrinolysis markers and hormonal markers, have all been linked to poorer cognitive and physical functioning, as well as mortality.

Although experienced individually, stress is inflected by its social context, and prospective population studies have found associations between measures of social support and mortality, psychiatric and physical morbidity and adjustment to and recovery from chronic disease. Interventions designed to alter the social environment and interpersonal relationships have been successful in facilitating psychosocial adjustment to medical disorders.

Social context is also relevant to the concept of well-being. Positive health is often regarded as the absence of illness, despite the fact that, half a century ago, the World Health Organization defined health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [6]. Ryff and Synger [7] remark that, historically, health is equated with the absence of illness rather than the presence of wellness. Research on psychological well-being has indicated that it depends on the interaction of several intercorrelated dimensions and plays a buffering role in coping with stress, with a favorable impact on the course of a disease.

Some diseases are clearly partially self-induced and there is a growing awareness that certain personality habits, such as smoking cigarettes, drinking alcohol and eating a diet rich in cholesterol and saturated fats, are highly likely to have an impact on health. Beliefs about risks associated with certain health-damaging behaviors are not necessarily associated with the absence of those risk behaviors. In a survey of health behaviors in young adults in eight European countries, those who drank and smoked were just as well aware of the negative consequences of these health-damaging behaviors as those who did not engage in these habits. On the other hand, beliefs about the positive effects of health-protective behaviors, such as eating a low-fat diet, exercise and participating in health screening exams (e.g. testing for breast or prostate cancer) were strongly associated with their practice.

Primary care physicians and medical practitioners rarely assess these psychosocial factors that have a strong potential to influence individual vulnerability to illness. However, and especially when symptoms lack an adequate physical explanation, even after a reasonable work-up, the physician must evaluate the specific contribution of life stress.

First it is important to seek a temporal relationship between life events and symptom onset or relapse. The loss of a body part or bodily function can induce grief reactions. Gradual changes which occur with chronic progressive disease may give the individual time to perceive and tolerate the changes, whereas sudden modifications are potentially more disruptive and grief-inducing.

Does the patient perceive the environment as exceeding his or her resources (allostatic load)? Often patients deny a relationship between their allostatic load and symptomatology, because they are unaware of the latency between stress accumulation and symptom onset ("I had bowel symptoms yesterday, which was an easy day at work, and not the previous days, which were awful"). Symptomatic worsening during weekends and vacation time is a common manifestation of this latency.

Another area that may need exploring is the presence of physical and/or sexual abuse at some point in the patient's life, while there is also a need to assess whether interpersonal relationships are providing a buffering role for stress, and to identify the individual's psychological assets.

All this information may be crucial for managing patients with unexplained somatic symptoms, in difficult patient-doctor relationships or when laboratory findings are borderline (e.g. slightly elevated prolactin levels). It requires a sensitive interviewing technique on the part of the physician, in some cases combined with self-rating inventories and/or techniques of self-observation (self-monitoring of daily activities and recording of the observed findings in a diary) by the patient.

The assessment of psychosocial correlates of medical disease

Psychosocial and biological factors interact in a number of ways in the course of medical disease. Their varying influence determines the unique quality of the experience and attitude of every patient in any given episode of illness.

The potential relationship between medical disorders and psychiatric symptoms ranges from a purely coincidental occurrence to a direct causal role of organic factors – whether medical illness or drug treatment – in the development of psychiatric disturbances.

Major depression, for example, has emerged as an extremely important source of comorbidity in medical disorders, and may be associated with higher mortality, particularly in the elderly. The presence of depressive symptoms in association with chronic medical illness has been found to affect quality of life and social functioning, leading to increased health care utilization, and depression can have an impact on compliance. Many cases of "suicide by default" (i.e. due to the deliberate omission of therapeutic, dietary and other measures necessary to sustain life or prevent the progress of pathology) may mask a major depressive disorder. Examples include diabetic patients who stop taking insulin, those who resume strenuous work after myocardial infarction and those who withdraw from chronic hemodialysis.

Research has also suggested that depression may increase susceptibility to medical illness. The evidence is particularly impressive in cardiovascular disease, with clinical depression appearing to be an independent risk factor for coronary artery disease as well as affecting the mortality rate after myocardial infarction. Depression has also been suggested to be a marker of cardiac disease severity.

Functional, i.e. nonorganic, medical symptoms are extremely common in medical practice. Their association with depression has been consistent, regardless of the design of the study. Depressed patients tend to have more somatic symptoms than nondepressed individuals, and somatizers tend to be more depressed than patients with physical disease.

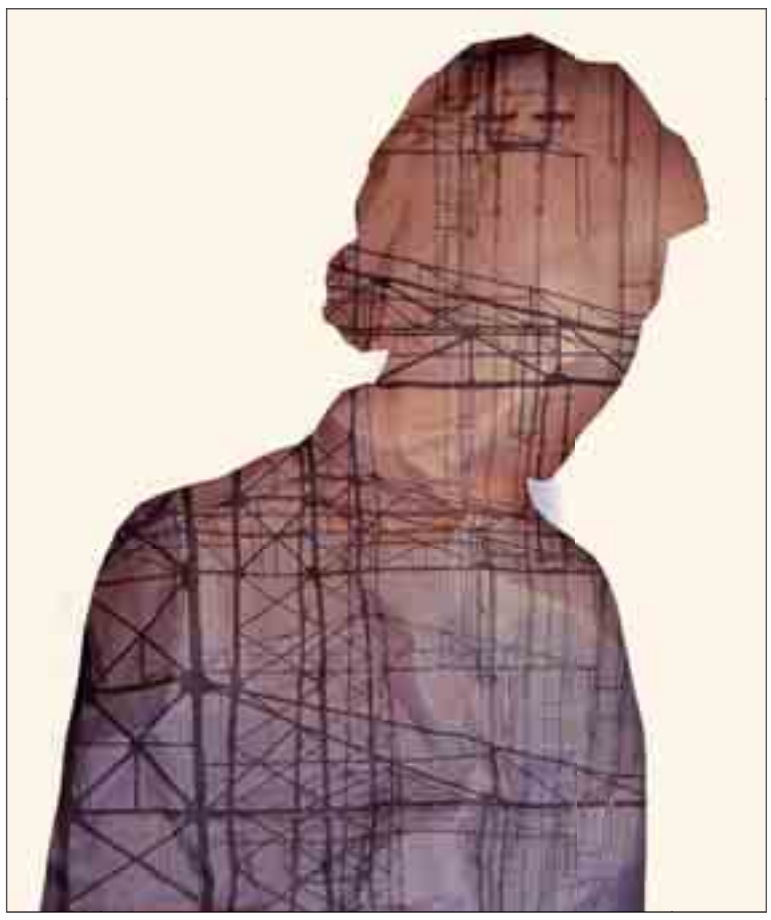
The current emphasis in psychiatry is on the assessment of symptoms resulting in syndromes identified by diagnostic criteria (DSM). However, there is an emerging awareness in psychiatry that psychological symptoms which do not reach the threshold of a psychiatric disorder can also affect quality of life and have pathophysiological and therapeutic implications. This is particularly true in the setting of medical disease, where most psychological symptoms cannot be assigned a suitable rubric according to psychiatric diagnostic criteria [4]. The case of hostility is exemplary here. A considerable body of evidence suggests a pathogenetic role for anger, hostility and irritable mood in physical illness. Hostility, in particular, has been identified as a risk factor for cardiovascular disease, particularly when associated with type A behavior (characterized by e.g. excessive work involvement, irritability and high competitiveness). In a similar manner, another psychological state – characterized by the giving-up complex, helplessness and hopelessness, and demoralization – has been found to facilitate the onset of disease to which the individual was predisposed.

Not surprisingly, diagnostic criteria based on psychological dimensions and subclinical clusters were found to be more suitable than DSM-IV criteria in identifying distress and impaired quality of life in medical populations [4].

Lipowski notes that once the symptoms of a somatic disease are perceived by a person or he or she has been told by a doctor that they are ill even if symptoms are absent, then this disease-related information gives rise to psychological responses which influence the patient's experience and behavior as well as the course, therapeutic response and outcome of a given illness episode [2]. The study of illness behavior, defined as the ways in which individuals experience, perceive, evaluate and respond to their own health status, has yielded important information. It also gave rise to Pilowsky's concept of abnormal illness behavior, characterized as the persistence of a maladaptive mode of perceiving, experiencing, evaluating and responding to one's health status, despite the fact that a doctor has provided a lucid and accurate appraisal of the situation and management to be followed, with opportunities for discussion, negotiation and clarifica-

Table 1. Nonspecific therapeutic ingredients that are shared by most forms of psychotherapy [10]

	Ingredient	Characteristics
1.	Attention	The therapist's full availability for specific periods.
2.	Disclosure	The patient's opportunity to ventilate thoughts and feelings.
3.	High arousal	An emotionally charged, confiding relationship with a helping person.
4.	Interpretation	A plausible explanation of the symptoms.
5.	Rituals	A ritual or procedure that requires the active participation of both patient and therapist and that is believed by both to be the means of restoring the patient's health.



tion, based on adequate assessment of all relevant biological, psychological, social and cultural factors [8]. The two main forms of abnormal illness behavior (illness affirming and illness denying) have several common expressions in clinical practice. They range from hypochondriasis and disease phobia to illness denial and lack of compliance.

Quality of life, particularly in chronic diseases, has become the focus of an increasing number of publications. While there is neither a precise nor agreed definition of quality of life, research in this area seeks essentially two kinds of information: the functional status of the individual and the patient's appraisal of health. The concept stems from the fact that measures of disease status alone are insufficient to describe the burden of illness and that the subjective perception of health status (e.g. lack of well-being, demoralization, difficulties fulfilling personal and family responsibilities, and so on) is as valid as that of the clinician in evaluating outcomes [4].

All the above considerations demonstrate that psychiatric illness, psychological disturbances and abnormal illness behavior can have a profound effect on quality of life and how the disease process is experienced. This calls for a comprehensive assessment of psychosocial aspects of medical disease, which cannot be equated to a standard psychiatric evaluation and may be particularly suitable for the following clinical situations.

(1) ***Somatization***. The tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them is a widespread clinical phenomenon that may involve up to 30–40% of medical patients. It may well be the most costly comorbidity. Fourteen common physical symptoms are responsible for almost half of all primary care visits, but only 10–15% are found to be caused by an organic illness over a 1-year period. Moreover, a significant proportion of problems presenting to a primary care physician cannot be assigned a suitable diagnostic rubric [4].

(2) ***Partial response to treatment***. Quality of life may often be compromised even when the patient is apparently doing well. Research on quality of life has indeed emphasized the discrepancies in health perceptions between patients, their companions and their treating physicians. In clinical medicine there is in fact the tendency to rely exclusively on "hard data," preferably expressed in the dimensional numbers of laboratory measurements, excluding "soft information," such as impairments and well-being. This soft information can now, however, be reliably assessed by clinical rating scales and indices [9].

(3) ***Suspected psychiatric complications of medical illness***. Timely recognition of psychiatric disorders which need specific treatments may have favorable implications for quality of life and disease course.

(4) ***Abnormal illness behavior***. Several manifestations of abnormal illness behavior (from hypochondriasis to lack of compliance) may hinder the prevention and treatment of medical disorders.

Application of psychological therapies to medical disease

Psychological interventions in the medically ill encompass the use of psychotherapeutic strategies and psychopharmacological interventions. They may be performed by a whole range of health professionals, including psychiatrists, psychologists, nurses and primary care physicians.

The progression of severe medical disorders is often linked to specific lifestyle behaviors. In the 1990s, the benefits of modifying lifestyle were demonstrated in coronary heart disease, and more recently, several major controlled clinical trials have shown that type 2 diabetes can be delayed or prevented by lifestyle modification, such as diet and exercise, in people at high risk. A number of psychological treatments, including cognitive-behavioral therapy, have also been shown to be effective in health-damaging behaviors, such as smoking. There is, in addition, a complex relationship between psychological well-being and physical exercise, which needs to be considered for both promoting physical activity and in preventing its excess.

Psychiatric disorders, and particularly major depression, frequently go unrecognized and untreated in medical settings, with widespread harmful consequences for the individual and society. Treatment of psychiatric comorbidity, such as depression, with either pharmacological or psychotherapeutic interventions, markedly improves depressive symptoms, health-related functioning and the patient's quality of life.

In controlled investigations for a number of medical disorders, the use of psychotherapeutic strategies, such as cognitive-behavioral therapy, stress management procedures and brief dynamic therapy, has yielded a substantial improvement in quality of life, coping or the course of the disease. Examples of these strategies are interventions that increase social support and enhance coping in patients with breast cancer and malignant melanoma, or writing about stressful experiences in asthma and rheumatoid arthritis. The results are not always favorable, however, and may depend on the type of psychosocial intervention and the specific populations. Nevertheless, research on psychotherapy has disclosed some common therapeutic ingredients that most psychotherapeutic techniques share, and these are outlined in table 1. Routine medical practice would also benefit from the presence of some – indeed perhaps all – of these features.

For many years, abnormal illness behavior has been viewed mainly as an expression of personality predisposition and considered to be refractory to treatment by psychotherapeutic methods. There is now evidence to challenge such a pessimistic stance. Several controlled psychotherapy studies, for example, have indicated that hypochondriasis is a treatable condition. By providing accurate information and the use of simple cognitive strategies, such as the clarification of previous faulty communications with physicians and common psychophysiological reactions (patients may in fact be unable to attribute somatic symptoms to anxiety), it is possible to deal with the hypochondriasis. Similarly, the application of simple suggestions has yielded significant improvements in controlled studies concerned with functional medical disorders. The correlation between abnormal illness behavior and health habits may have implications in preventive efforts. Indeed, individuals with hypochondriacal fears and beliefs were found to take worse care of themselves than control subjects in several studies. They may be so distressed by their belief that they have an undiagnosed or neglected disease that choices that may yield benefits in the distant future appear to be irrelevant to them.

Psychosomatic treatment consists of the integration of psychological interventions (brief individual psychotherapy, behavioral techniques, group psychotherapy) and psychopharmacology with conventional medical treatments. It appears to be particularly warranted when there is refractoriness to lifestyle modifications guided by primary care or other nonpsychiatric physicians; in the presence of psychological disturbances (e.g. demoralization and irritable mood) or psychiatric illness (such as major depression or panic disorder); in the presence of abnormal illness behavior interfering with treatment or leading to repeated health care utilization, such as illness denial or hypochondriasis, and in patients with an impaired quality of life and functioning that is not justified by the medical condition.

A new medicine

Psychosomatic medicine needs to be incorporated into clinical practice. How an individual functions in daily life, his or her productivity, performance of social roles, intellectual capacity, emotional stability and well-being have all emerged as crucial components of clinical investigation and patient care. These issues have become particularly important in chronic diseases which cannot be cured and also extend to such patients' caregivers – whose emotional burden has become increasingly manifest – and health providers. Patients have certainly become more aware of these problems, and their difficulties in coping with medical illness and its psychological consequences have led to the establishment of many patients' associations. On the other hand, there is also increasing emphasis on health promotion rather than simple disease prevention. The commercial success of books on complementary medicine and positive practices as well as the upsurge of interest in mind-body medicine exemplify the receptivity of the general public to messages of health prevention and alternative medical models. Psychosomatic interventions can respond to these emerging needs and may play an important role in supporting the healing process.

A significant proportion of morbidity and premature mortality in the US can be attributed to "largely preventable behaviors and exposures," such as tobacco smoking, obesity and physical inactivity [11]. Yet almost all (95%) of health care spending is directed at biomedically oriented care, even while, simultaneously, the proliferating connections between physicians and the pharmaceutical industry have brought the credibility of clinical medicine to an unprecedented crisis [12]. The exponential spending on preventive pharmaceuticals, justified by the potential long-term benefits to a very small segment of the population, is highly questionable [13], while the traditional boundaries among medical specialties, based mostly on organ systems (e.g. cardiology, gastroenterology) appear to be increasingly inadequate to deal with symptoms and problems which cut across organ system subdivisions and require a holistic approach [12].

As Noam Chomsky reminds us, "if we do not like what we see when we look in the mirror honestly, we have every opportunity to do something about it" [14]. If we do not like what we see in medicine today, we should remember that a different medicine is possible. It is called psychosomatic medicine.

About the author

Giovanni A. Fava received his MD degree from the University of Padua in 1977. He is currently Professor of Clinical Psychology at the University of Bologna and Clinical Professor of Psychiatry at the State University of New York at Buffalo. Since 1991, he has been editor-in-chief of *Psychotherapy and Psychosomatics* and serves on the editorial board of *Advances in Psychosomatic Medicine* and several other journals. He has performed groundbreaking research in psychosomatic medicine, cognitive behavioral therapy and mood and anxiety disorders.

References

1 Engel GL: The need for a new medical model: a challenge for biomedicine. Science 1977;196:129–136.
2 Lipowski ZJ: Psychosomatic medicine: past and present. Can J Psychiatry 1986;31:2–21.
3 Kissen DM: The significance of syndrome shift and late syndrome association in psychosomatic medicine. J Nerv Ment Dis 1963;136:34–42.
4 Fava GA, Sonino N: The clinical domains of psychosomatic medicine. J Clin Psychiatry 2005;66:849–858.
5 McEwen BS, Stellar E: Stress and the individual: mechanisms leading to disease. Arch Intern Med 1993;153:2093–2101.
6 World Health Organization: World Health Organization constitution. Geneva, World Health Organization, 1948, p. 28.
7 Ryff CD, Singer B: Psychological well-being. Psychother Psychosom 1996;65:14–23.
8 Pilowsky I: Abnormal Illness Behaviour. Chichester, Wiley, 1997.
9 Nierenberg AA, Sonino N (eds): From Clinical Observations to Clinimetrics: A Tribute to Alvan R. Feinstein, MD. Psychother Psychosom 2004;73:129–196.
10 Fava GA, Sonino N: Psychosomatic medicine. Psychother Psychosom 2000;69:184–197.
11 Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. JAMA 2004;291:1238–1245.
12 Fava GA: A different medicine is possible. Psychother Psychosom 2006;75:1–3.
13 Heath I: Combating disease mongering. PloS Med 2006;3:e146.
14 Chomsky N: Universals of human nature. Psychother Psychosom 2005;74:263–268.

The Placebo and Nocebo Effect: How the Therapist's Words Act on the Patient's Brain

Fabrizio Benedetti

Department of Neuroscience, University of Turin Medical School, and National Institute of Neuroscience, Turin, Italy

Clinicians have long known that the context surrounding a therapy is important in any medical treatment and that the words and attitudes of doctors and nurses can have a great impact on the patient. The importance of the verbal interaction between professional personnel and those in their care is illustrated by the emotional impact an anesthetist can have on his or her patient: postoperative pain and narcotic intake were reduced in patients who had been informed about the possible course of their pain following surgery and encouraged to overcome it, compared to a group of patients who had not received a presurgery visit and reassuring words from the anesthetist [1].

In another study performed in the 1980s, patients were given different verbal information in general practice consultations. In positive consultations, if no prescription was to be given, they were told that they required none, and if a prescription was to be given, that the therapy would certainly make them better. Conversely, in negative consultations, no firm assurance was given. In fact, if no prescription was to be given, the following statement was made: "I cannot be certain what your problem is, therefore I will give you no treatment." Conversely, if a prescription was to be given, the patients were told: "I am not sure that the treatment I am going to give you will have an effect." The treatment was a placebo (an inert substance with no pharmacological action) in both the positive and negative consultations. Two weeks after consultation, recovery was significantly greater in the positive than in the negative group, but there was no difference between the treated and untreated groups, thus indicating that the words the doctor used were critical for recovery [2].

In a similar study, postoperative patients were treated with a painkiller on request, for 3 consecutive days, and with a basal infusion of an inert solution with no pharmacological action (placebo) [3]. However, the symbolic meaning of this basal infusion varied in three different patient groups. The first group was told nothing, the second was told that the infusion could be either a potent analgesic or a placebo, and the third group was told that the infusion was a potent painkiller. Thus the second group received uncertain verbal information ("It can be either a placebo or a painkiller. Thus we are not certain that the pain will subside."), whereas the third group received clearcut information ("It is a painkiller. Thus pain will subside soon."). It was found that the intake of the painkiller decreased in the second group compared with the first, and even more in the third group. In fact, the reduction in painkiller requests in the second group was as large as 20.8% compared with the first group, and the reduction in the third group was even larger – 33.8%. It is important to point out that the time course of pain was the same in the three groups over the 3-day period of treatment. Thus the same analgesic effect was obtained with different doses of the painkiller.

What all these studies show is that the therapist's words can be of crucial importance in the therapeutic outcome. They can increase the efficacy of a treatment, can reduce the intake of some drugs, and can improve the patient's quality of life. Therefore, the therapist's words, and more generally the psychosocial context around the therapy, may affect both the patient's mind and body.

Placebo and nocebo effects

Placebo and nocebo effects represent a very good model to understand how the therapist's words act on the patient's brain. A placebo [Lat.: "I shall please"] is a simulation of a medical intervention, be it pharmacological or not, and it has no specific action on the disease to be treated. The placebo effect is the outcome that follows the administration of a placebo. For example, we can simulate an analgesic therapy by giving the patient a sugar pill or a glass of fresh water along with the verbal suggestions that it is a powerful painkiller. The essential point here is that the patient trusts the doctor, believes in the treatment and thus expects a clinical benefit. The placebo effect is, therefore, the effect of the psychosocial context around the therapy, particularly its verbal component, on the patient's brain (fig. 1). In other words, the psychosocial context may induce expectations of clinical improvement which, in turn, may affect the course of a symptom or a disease.

The effect of a nocebo [Lat.: "I shall harm"] is the reverse of the placebo effect. Expectations of clinical worsening may induce a real worsening, such as an increase in pain. Therefore, it is important to understand that neither sugar pills nor glasses of water will ever acquire the capacity to heal. What matters are the words that are administered along with the sugar or water.

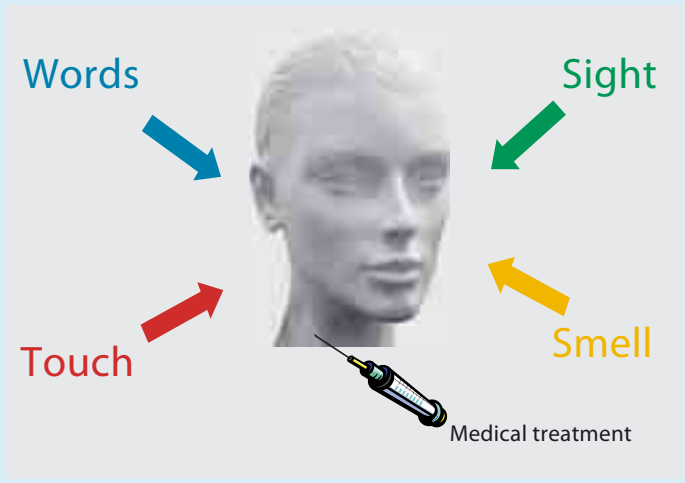


Fig. 1. When a medical treatment, for example the injection of a drug, is administered, there is a complex context around the patient and the therapy which tells the patient that a therapy is being carried out: the sight of the environment, the smell of drugs, the doctor's words, the touch by needles, and such like. This context may play a crucial role in the therapeutic outcome by inducing expectations of clinical benefit.

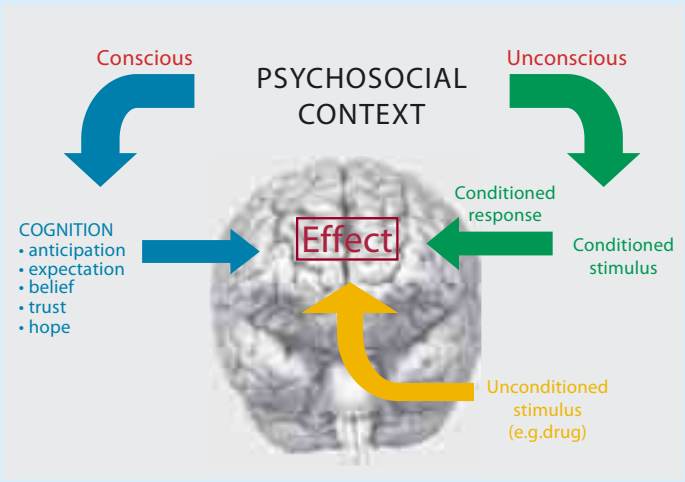


Fig. 2. The psychosocial context may act on the patient's brain through an unconscious conditioning mechanism whereby, after repeated associations between the context itself (conditioned stimulus) and the drug action (unconditioned stimulus), the context alone may produce an effect. The psychosocial context may also act through complex cognitive factors, such as anticipation and expectation of an outcome, beliefs, trust and hope.

Until about a decade ago, most placebo research employed the methods and techniques of both experimental and social psychology. For example, most research was devoted to an understanding of expectation and conditioning mechanisms. In the first case, it has been shown that complex cognitive factors such as expectation and anticipation of clinical benefit, beliefs, trust and hope, are important and essential in some conditions. In the second case, a mechanism of classical conditioning has been found to play a crucial role in other situations: contextual cues, like the color and shape of pills, may act as a conditioned stimulus that, after repeated associations with an unconditioned stimulus, e.g. the painkiller contained in the pills, is alone capable of inducing analgesia (fig. 2).

With the advent of modern techniques and methods for investigating the human brain, like neuropharmacology, brain imaging and single-neuron recording in awake patients, neurobiologists became interested in understanding what happens in the brain of subjects who receive a placebo, in other words, who expect a therapeutic benefit. This neurobiological approach is paying dividends, as we are now beginning to understand better the intricate cascade of biological events that take place in the brain during a placebo response. It therefore goes without saying that the placebo/nocebo phenomenon represents an interesting and promising model to clarify some aspects of the mind-body interaction, whereby a complex mental activity, like the expectation of a future outcome, activates specific neuronal systems.

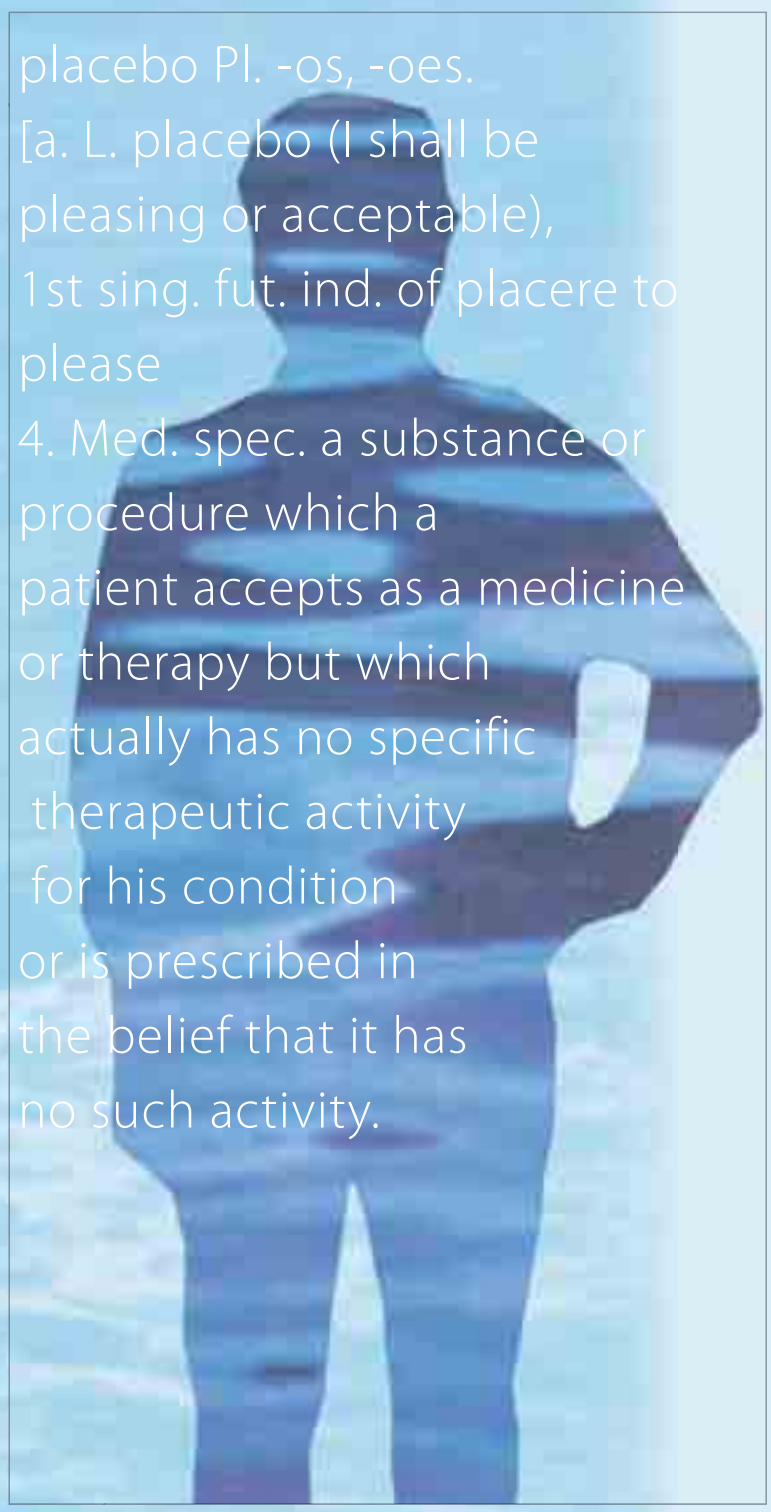
Placebos and nocebos move many molecules in the brain

When we give either a placebo or a nocebo, basically we administer verbal suggestions of either improvement or worsening. Words are very important, and indeed most placebo and nocebo research investigates verbally induced placebo and nocebo responses. However, words are not the only means to induce expectations: the healing environment, the attitudes of the medical personnel, beliefs and trust in medical procedures, can all induce expectations of a therapeutic outcome.

The key questions are: What happens in patients' brains when they expect a clinical improvement or worsening? Are specific brain networks activated? What is the clinical relevance of understanding these mechanisms?

As far as the mechanisms are concerned, today we know that the administration of placebos and nocebos activates many molecules in the patient's brain. Most of our knowledge about these mechanisms comes from studies on pain and analgesia, and a summary of the complex cascade of biochemical events following placebo administration and inducing placebo analgesia is provided in figure 3. First of all, there is today general agreement that the endogenous opioid systems play an important role in some circumstances, and several lines of evidence indicate that placebo analgesia is mediated by a pain-modulating network which uses endogenous opioids as neuromodulators. This experimental evidence comes from a combination of both pharmacological and brain-imaging studies.

Supporting the involvement of endogenous opioids are a number of pharmacological studies which show that placebo analgesia is antagonized by the opioid antagonist naloxone. In other words, it is possible to prevent the placebo analgesic response by blocking the brain opioid receptors [4]. Using positron emission tomography (PET), a technique that assesses metabolic activity and physiological functions in the brain, it was found that the very same regions in the brain are affected by both a placebo and an opioid drug, thus indicating a related mechanism in placebo-induced and opioid-induced analgesia [5]. In particular, the administration of a placebo induces the activation of the rostral anterior cingulate cortex, the orbitofrontal cortex and the brainstem. Moreover, there is significant covariation in activity between the rostral anterior cingulate cortex and the lower pons/medulla at the level of the rostral ventromedial medulla, and subsignificant covariation between the rostral anterior cingulate cortex and the periacqueductal gray, suggesting that the descending



"cingulate cortex/periacqueductal gray/ventromedial medulla" pain-modulating circuit is involved in placebo analgesia (fig. 4). In another study using functional magnetic resonance imaging, a technique similar to PET, brain activation patterns in the prefrontal lobes changed in anticipation of analgesia following placebo administration, and regions involved in pain transmission decreased their activity during the placebo response (fig. 4). Only recently, activation of the endogenous opioid systems by placebo administration was documented directly using PET and in vivo receptor binding in humans [6].

The placebo-activated endogenous opioids act not only on pain transmission but on the respiratory centers as well, inducing a placebo respiratory depressant effect, which mimics the typical side effect of opioid drugs. Likewise, placebo-activated endogenous opioids affect the cardiovascular system, slowing down the activity of the heart during placebo analgesia. The placebo-activated endogenous opioids have also been shown to interact with endogenous substances that are involved in pain transmission. In fact, on the basis of the anti-opioid action of cholecystokinin (CCK), CCK-antagonist drugs have been demonstrated to enhance placebo analgesia, suggesting that the placebo-activated opioid systems are counteracted by CCK during a placebo response [4].

Some types of placebo analgesia appear to be mediated by neuromodulators other than opioids. For example, if a placebo is given after repeated administrations of a nonopioid painkiller, the placebo analgesic response is not mediated by endogenous opioids. In addition, placebo-induced activation of growth hormone and inhibition of cortisol have been described after administration of the analgesic drug sumatriptan, an agonist of serotonin receptors, suggesting that placebos may also act on serotonin-dependent mechanisms [4].

The role of CCK seems to be particularly important in the nocebo hyperalgesic effect, although nocebo hyperalgesia (i.e. the induction of increased pain) is still little understood. This effect can be blocked by proglumide, a drug that blocks CCK receptors in the brain, indicating that nocebo hyperalgesia is mediated by CCK. Since CCK plays a role in anxiety and a nocebo procedure itself is anxiogenic, these findings imply that proglumide acts on a CCK-dependent increase of anxiety and pain during a nocebo procedure [4].

Although pain is the best known model to study placebo and nocebo effects, other conditions are now providing further insight into the biological mechanisms of placebos and nocebos. For example, patients who suffer from Parkinson's disease have been shown to release dopamine after placebo administration [7] and also demonstrated changes in neuronal activity in the basal ganglia (fig. 5) [6]. Similar to the procedure in pain studies, patients were given an inert substance (placebo) and told they were receiving an anti-Parkinsonian drug that would produce an improvement in their motor performance. According to one hypothesis, the placebo-induced release of dopamine in Parkinson's disease is related to reward mechanisms. In this case, the reward would be the clinical benefit.

The neural mechanisms of placebo treatments have also been studied in depression, although the underlying mechanisms are poorly understood [6]. Depressed patients who receive a placebo treatment show both electrical and metabolic changes in the brain. In the first case, placebos induce electroencephalographic changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere. In the second case, changes in brain glucose metabolism were measured by PET in subjects with unipolar depression. Placebo treatments were associated with metabolic changes in different brain areas. Interestingly, these areas were also affected by the selective serotonin reuptake inhibitor fluoxetine, a result that suggests a possible role for serotonin in placebo-induced antidepressant effects.

Reduced effectiveness of hidden therapies

Some of the best evidence that expectations affect therapeutic outcome comes from studies on hidden therapies, in which patients do not know that any treatment is being given and thus do not expect any response or result. It is possible to perform a hidden infusion of a drug using a computer-controlled infusion pump which is preprogrammed to deliver the drug at a desired time. The crucial point here is that the patient does not know that any drug is being injected. The computer-controlled infusion pump can deliver a painkiller automatically, without any doctor or nurse in the room, and with the patient completely unaware that a treatment

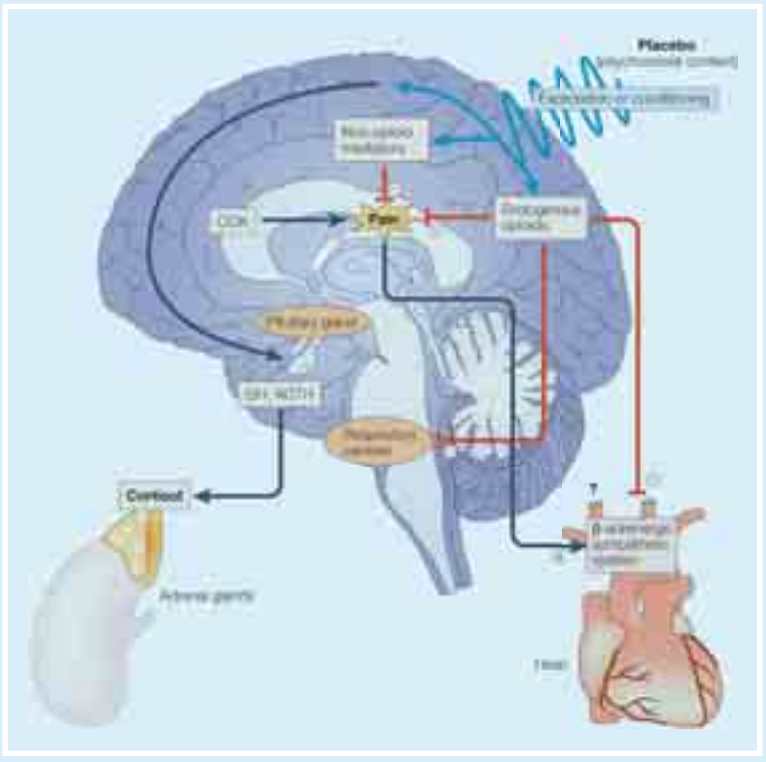


Fig. 3. Cascade of biochemical events that may occur in the brain after placebo administration. Placebo administration, along with verbal suggestions of analgesia (psychosocial context), might reduce pain through opioid and/or nonopioid mechanisms by expectation and/or conditioning mechanisms. The respiratory centers might also be inhibited by endogenous opioids. The β-adrenergic sympathetic system of the heart is also inhibited during placebo analgesia, although the underlying mechanism is not known (either reduction of the pain itself or direct action of endogenous opioids). Cholecystokinin (CCK) counteracts the effects of the endogenous opioids, thereby antagonizing placebo analgesia. Placebos can also act on serotonin-dependent hormone secretion, in both the pituitary and adrenal glands, thereby mimicking the effect of the analgesic drug sumatriptan. ACTH, adrenocorticotrophic hormone; GH, growth hormone. [Reproduced from ref. 4.]

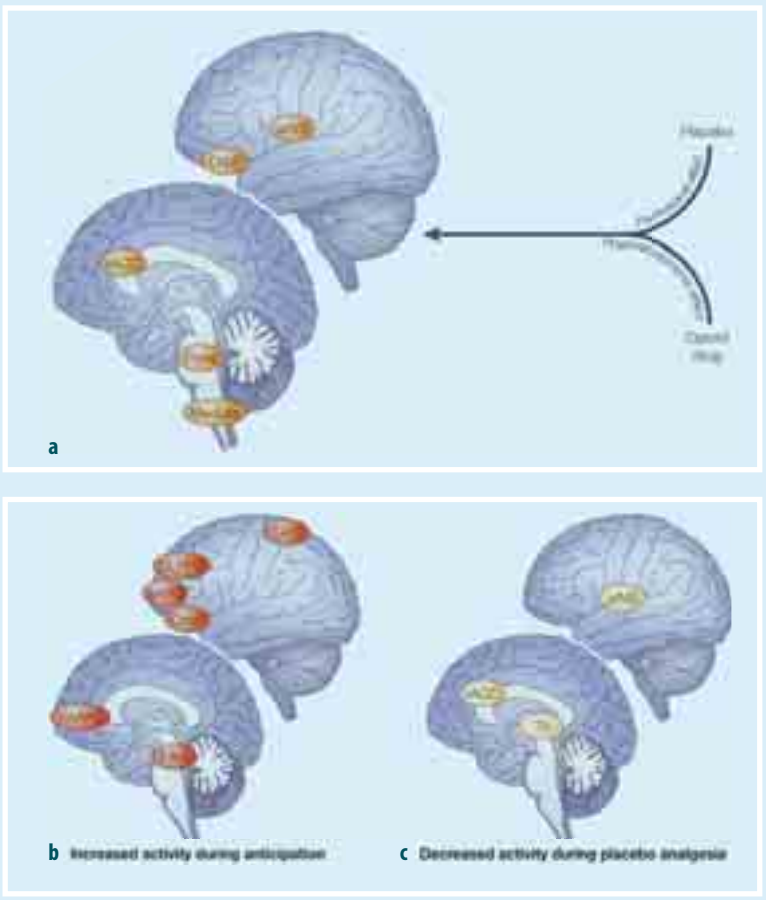
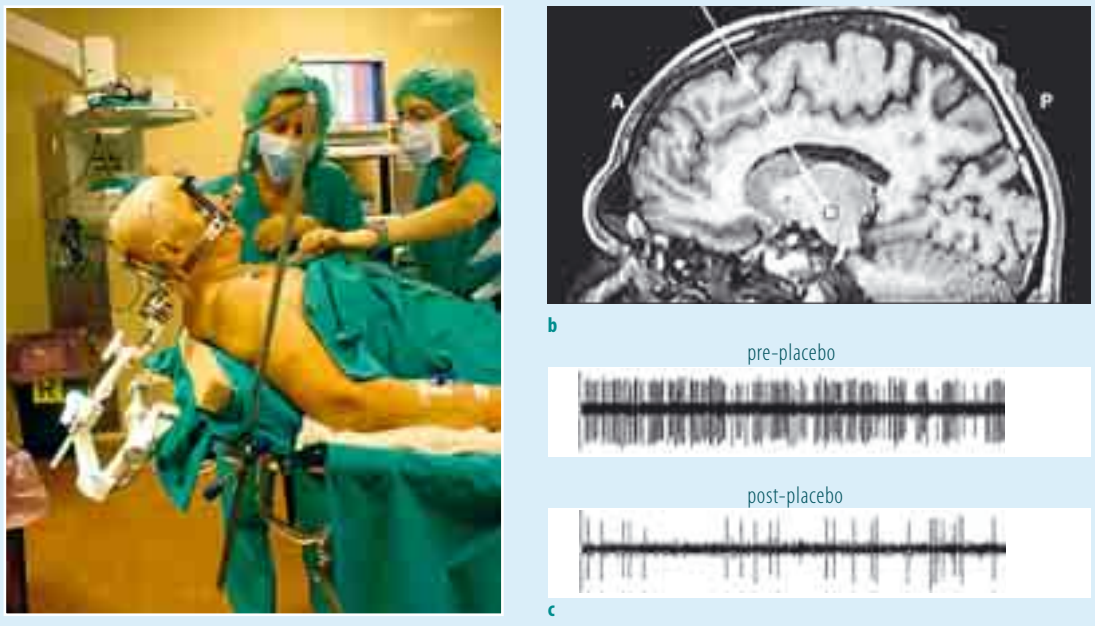


Fig. 4. Summary of brain-imaging studies of placebo analgesia [4]. **a**. Brain regions activated by the administration of a placebo and the administration of an opioid drug, indicating that mental events (psychosocial effect) and painkillers (pharmacodynamic effect) might have similar effects on the brain. **b**. During the anticipatory phase, the activated brain regions are likely to represent the activation of a cognitive-evaluative network. **c**. During placebo analgesia, the activity of different brain areas involved in pain processing decreases, which indicates an effect of the placebo on pain transmission. aAPC, anterior anterior prefrontal cortex; aINS, anterior insula; DLPFC, dorsolateral prefrontal cortex; OrbF, orbitofrontal cortex; PAG, periacqueductal gray; rACC, rostral anterior cingulate cortex; rmAPC, rostral medial anterior prefrontal cortex; SPC, superior parietal cortex; Th, thalamus. [Reproduced from ref. 4.]

has been started. The outcome following a hidden, or unexpected, treatment is then compared to an open, or expected, treatment. The latter is performed according to routine medical practice, whereby the medical personnel administer a drug along with the reassuring words that the symptom is going to subside shortly [8].

In postoperative pain following oral surgery, a hidden injection of 6–8 mg of morphine was found to correspond to an open injection of placebo. In other words, telling a patient that a painkiller is being injected (actually a placebo) is as potent as 6–8 mg of morphine. An analgesic effect stronger than the placebo was only observed when the hidden morphine dose was increased to 12 mg. This suggests that an open injection of morphine in full view of the patient, which is the usual medical practice, is more effective than a hidden injection, because in the latter, the placebo component is absent [4]. An analysis of the differences between open and hidden injections in the postoperative setting has been performed recently. The effects of four widely used painkillers (buprenorphine, tramadol, ketorolac, metamizol) were analyzed following either open or hidden injections. The analgesic dose needed to reduce the pain by 50% was much higher with hidden infusions than with open ones for all four painkillers, indicating that a hidden administration is less effective than an open one. The time course of postoperative pain was also found to be significantly different between open and hidden injections. In fact, during the first hour after the injection, pain ratings were much higher with a hidden injection than with an open one (fig. 6) [8].

Similar results have been obtained in other conditions, such as anxiety and Parkinson's disease, indicating that pain is not a special case. Therefore, knowledge about a therapy by patients can make a difference, as it may affect the therapeutic outcome [8].



a b c

Fig. 5. Recording the activity of single neurons from the brain of an awake patient suffering from Parkinson's disease. Both the recording apparatus (**a**) and the electrode track (**b**) can be seen. In (**c**), the activity of a single neuron in the subthalamic nucleus can be seen before and after placebo administration.

The clinical impact

There are many clinical implications of these recent advances in the neurobiology of the placebo/nocebo effect. First of all, when we want to assess the efficacy of a new drug in a clinical trial, it is necessary to take certain points into consideration. First, we need to address the expectations of a patient in a clinical trial through the study of perceived assignment to a group (either placebo or active treatment) rather than the standard analysis of actual assignment. In other words, the patient's perceived assignment to a group in a clinical trial may have a greater impact on the outcome than the actual treatment itself.

Second, any pharmacological agent may interfere with the cascade of biochemical events triggered by expectations. In a clinical trial carried out in the 1990s, a group taking a placebo was compared with a group taking the CCK-antagonist, proglumide. The analgesic effect was greater in the proglumide than in the placebo group, suggesting that proglumide is a good analgesic. However, this conclusion is erroneous, because a hidden injection of proglumide is totally ineffective, demonstrating that it is not an analgesic, but that it enhances placebo-activated endogenous opioids. This finding means that, in light of the fact that some substances may interfere with placebo-activated endogenous opioids, we must consider that a new drug (like a CCK-antagonist) may have no analgesic properties in and of itself but may enhance placebo-activated endogenous opioids [4].

I believe that the trial described above exposes an urgent need to understand the neurobiological mechanisms of the placebo response. By borrowing the Heisenberg uncertainty principle from physics, which imposes limits on the precision of a measurement, we can apply a similar principle to the outcomes of clinical trials. In the same way that the uncertainty principle states that a dynamic disturbance is necessarily induced in a system by a measurement, a dynamic disturbance might be induced in the brain in clinical trials by almost any type of drug. The nature of this dynamic disturbance is the interference of the injected drug with the expectation biochemical pathways, with an effect on both the outcome measures and the interpretation of the data. One possible solution to this problem is a hidden injection of the drug to be tested, in order to eliminate all the biochemical events triggered by expectations.

Besides this impact on clinical trials, there are also important implications for routine medical practice. The studies on hidden therapies teach us that the knowledge about a therapy affects the therapeutic outcome. Therefore, clinicians should strive to communicate their therapeutic interventions to their patients in order to increase expectations and to trigger the activation of those molecules in the brain that mediate placebo responses. Interestingly, a disruption of expectation/placebo-related analgesic mechanisms may occur in a clinical condition, Alzheimer's disease, in which an impairment of cognition is associated with the loss of connectivity among different brain regions, particularly the frontal lobes. Alzheimer patients with frontal lobe impairment show reduced expectations and placebo effects, so that analgesic therapies have been found to be less effective [9]. These findings underscore the urgent need to consider a possible revision of the therapeutic approach in Alzheimer patients, such as a dose increase to compensate for the loss of the endogenous expectation and placebo mechanisms.

Understanding the biochemical bases of the nocebo effect has important implications as well. First, inducing negative expectations may worsen some symptoms and may interfere with recovery from a disease. Second, the identification of a neuromodulator of nocebo hyperalgesia, i.e. CCK, may lead to the development of new CCK-antagonists for the treatment of anxiety-related pain. Likewise, understanding the nocebo effect in other conditions may lead to new therapeutic strategies for various diseases.

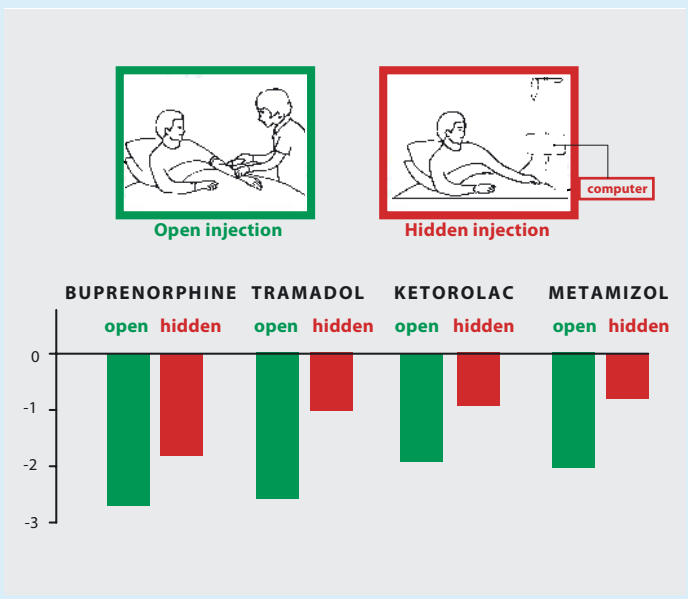


Fig. 6. An open injection is compared to a hidden injection of one of four painkillers. An open injection is performed by a doctor in full view of the patient, whereas a hidden injection is carried out by a computer with the patient completely unaware that a drug is being administered. In all cases, a hidden injection is less effective than an open one.

The future

The future challenge for placebo research is to expand our knowledge about placebo- and nocebo-related phenomena in different diseases, and in particular to refine our understanding about where, when and how placebos and nocebos act. This knowledge will provide us with important information on the functioning of our brain and body as well as on the possible implications and applications in the clinical setting. In the first case, the placebo/nocebo phenomenon promises to shed new light on the interaction between mind, brain and the body. In the second case, better neurobiological understanding may lead to improvements in clinical practice, including the therapist-patient interaction and different psychotherapeutic approaches.

Finally, we need to explore further the impact of placebo research on society in order to identify both the positive and negative aspects of the suggestibility of the human mind. If future research leads to a full understanding of the mechanisms of psychological suggestibility, an ethical debate will then be required to prevent the misuse of placebos and nocebos. There are, therefore, potentially negative outcomes of placebo research that need to be discussed and considered from an ethical perspective. I believe that these issues are worthy of intense scientific scrutiny and will lead to fundamental insights into human biology.

About the author

Fabrizio Benedetti obtained his MD degree at the University of Turin Medical School in Italy in 1981. He joined the Postdoctoral School of Psychiatry and Biobehavioral Sciences at the University of California in Los Angeles where he won the Silbert International Award. In the 1990s he was appointed Assistant Professor at the Southwestern Medical Center of the University of Texas in Dallas. He is now Professor of Physiology at the University of Turin Medical School. His current scientific interests are the placebo effect across diseases, pain in dementia, and intraoperative neurophysiology for mapping the human brain.

References

1 Egbert LD, Battit GE, Welch CE, Bartlett MK: Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med 1964;270:825–827.
2 Thomas KB: General practice consultations: is there any point in being positive? BMJ 1987;294:1200–1202.
3 Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F: Response expectancies in placebo analgesia and their clinical relevance. Pain 2001;93:77–84.
4 Colloca L, Benedetti F: Placebos and painkillers: is mind as real as matter? Nat Rev Neurosci 2005;6:545–552.
5 Petrovic P, Kalso E, Petersson KM, Ingvar M: Placebo and opioid analgesia – imaging a shared neuronal network. Science 2002;295:1737–1740.
6 Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK: Neurobiological mechanisms of the placebo effect. J Neurosci 2005;25:10390–10402.
7 de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ: Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 2001;293:1164–1166.
8 Colloca L, Lopiano L, Lanotte M, Benedetti F: Overt versus covert treatment for pain, anxiety and Parkinson's disease. Lancet Neurol 2004;3:679–684.
9 Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, Asteggiano G: Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. Pain 2006;121:133–144.

Posttraumatic Stress Disorder: A Mind-Body Response to Life-Threatening Events

Andreas Maercker

Department of Psychology, University of Zürich

Imagine: you are peacefully asleep in your bed when suddenly you are awakened by a voice that says, "I have a knife, so don't make any noise." You wonder if you are having a nightmare but as you awaken more fully, you feel the point of the knife at your throat. You begin to hyperventilate as you experience complete terror. You feel frozen — both mentally and physically.

This is an example of an event that nearly everyone would find traumatic – a sudden, unexpected, life-threatening assault. When researchers began studying traumatic stress, and in particular posttraumatic stress disorder (PTSD), they assumed that the psychological and biological processes would be related in essential ways to the normal response to stress. However, while normal stress responses are acute reactions that quickly return to homeostasis, the mind and body responses in PTSD reflect chronic and often increasing changes over time. Even when stress is chronic, the results differ from those of traumatic stress. The effects of chronic stress develop slowly over time, whereas the effects of traumatic stress are sudden and dramatic and are marked by fear, helplessness and horror.

PTSD was first labeled as such in 1980, following the Vietnam War. Prior to that time, there had been only periodic interest in traumatic stress, usually in times of armed conflict, and it was known under various names, such as traumatic neurosis, shell shock or concentration camp syndrome. PTSD, however, has gained increasing attention in the last quarter of a century with the rise in military missions abroad, natural disasters, technical and traffic accidents, and domestic violence – the latter, though, still given short shrift in most PTSD studies.

What is PTSD?

According to the contemporary diagnostic systems for psychiatric disorders, six criteria must be met before a diagnosis of PTSD can be made. The first, criterion A, is the stressor criterion. It states that a person must have experienced, witnessed or been confronted with an event that involved actual or threatened death or serious injury, or a threat to the physical integrity of the person or others.

The second criterion, B, reflects reexperiencing symptoms. The most dramatic form of reexperiencing is the flashback. Here the patient feels and acts as if the trauma is recurring. Reexperiencing also includes distressing memories or dreams (nightmares) when faced with stimuli linked to the traumatic event. There may be physiological or psychological stress reactions – including full-blown panic attacks – associated with this reexperiencing.

Avoidance and numbing symptoms comprise the third criterion, C. Patients with PTSD may attempt to avoid trauma-related thoughts or activities. They may show a notably diminished capacity to experience pleasure, difficulty in remembering aspects of the trauma, blunted affect and feelings of detachment or estrangement from others.

Symptoms of hyperarousal and hypervigilance are represented in criterion D. They include pervasive arousal that is reflected by difficulties in concentration, irritability and problems in falling and staying asleep. Also included are exaggerated startle responses to a variety of cues.

The fifth criterion, E, for the diagnosis is that the B, C and D symptoms persist for at least 1 month. The sixth criterion, F, is that this combination of symptoms causes significant distress for the person or impairment in his/her social or professional functioning. Criterion F specifies that a diagnosis of psychopathology should not be made if the symptoms are mild or do not really interfere with a person's life.

When the PTSD diagnosis was introduced in 1980, it was believed that traumatic events sufficient to induce this condition would be rare. However, subsequent epidemiologic surveys have documented a high prevalence of such events, with one- to two-thirds of the population receiving exposure to trauma over the course of a lifetime. In first world countries, the most common traumatic events are witnessing a severe injury or death and/or involvement in a fire, other natural disaster or life-threatening accident. Rape, sexual and physical abuse, and parental neglect are more common among women than men. Men are more likely to experience physical attack or military-related trauma.

In countries of the northern hemisphere, the lifetime prevalence of PTSD (i.e. the chance of suffering PTSD at least once during one's life) is approximately 5%. The rate is obviously significantly higher in war-stricken countries or countries with especially high rates of crime or natural catastrophies.

PTSD is not the only psychiatric disorder that may develop after a traumatic experience. Depression and anxiety disorders may result independently of PTSD or may be comorbid with it. Clinicians often observe that other disorders develop as maladaptive coping attempts and then become full-blown problems in and of themselves. For example, if someone has severe PTSD symptoms including nightmares, sleep disruption, flashbacks, hypervigilance and other physiological arousal symptoms, that person may attempt to reduce his/her suffering by consuming alcohol or illegal drugs. Not uncommonly, somatic diseases may be comorbid with PTSD. Studies in the elderly have reported direct links between trauma and a broad spectrum of medical conditions (diabetes mellitus, heart disease, obesity and osteoarthritis) in 20- or 30-year follow-ups of men initially exposed to traumatic stress.

This brings us to the point where we can begin to consider the numerous ways in which the mind and body interact in PTSD. This relationship functions in all stages of the development and manifestation of PTSD, from risk and resilience factors through to the core psychobiological changes associated with PTSD. The development of successful therapies for PTSD is also fundamentally dependent on understanding how the mind and body can synchronously and mutually respond to and cope with real and perceived threats to their integrity.

Early life trauma as a risk factor

Because people show varying responses to similar traumatic events, it is likely that the trauma itself is not solely responsible for causing the posttrauma symptoms. This realization has led to the search for factors that may increase the risk of developing PTSD after trauma. One such factor that has recently received considerable attention from researchers is the victim's psychological history or prior experience with trauma.

Until the last decade, the hypothesis that early life trauma is associated with an increased risk of adult PTSD or other psychiatric disorders was supported largely by anecdotal reports inspired by psychoanalytic concepts of early critical periods of development. The best research in the neurobiology of depression has commonly found indications of early life stress. How about the role of early life trauma in victims who develop PTSD?

Valid data to examine the correlation between early trauma and later PTSD (or depression) are, in fact, surprisingly sparse and are derived mainly from small samples or spontaneous reports of trauma from social service departments or hospital emergency rooms. Reported cases of early trauma constitute a relatively small fraction of all cases; however, although prevalence estimates of childhood abuse and other traumas such as early loss of parents are extremely approximate, they are indeed sufficient to account in part for the development of PTSD after trauma (or depression) among the general adult population.

A study in the USA by McCauley and colleagues [1] of nearly 2,000 women from all socioeconomic classes attending four community-based primary care internal medicine practices found a 22% prevalence of reported childhood or adolescent physical or sexual abuse or severe neglect. Compared with the remainder of the sample, those with childhood trauma reported significantly more physical symptoms, as well as significantly higher scores for depression, anxiety, somatization and interpersonal sensitivity, a fivefold higher prevalence of drug abuse and a twofold higher level of alcohol abuse. Unfortunately, PTSD diagnoses were not studied.

More recently, we investigated a representative sample of approximately 2,000 young women from Dresden (Germany) for the occurrence of traumatic events and the development of PTSD and depression [2]. Although the prevalence of childhood trauma of 11% was lower than in the US study, risks for PTSD and depressive disorder were 17% and 23%, respectively. Interestingly, the equal risk of later PTSD or depression is in line with other research findings on psychopathological vulnerability in humans.

By and large, these data support the general models of vulnerability to PTSD or depressive disorder which posit that genetic factors, temperament, and trauma early and later in life markedly increase the risk of these conditions. When superimposed on this background of risk, recently experienced traumatic events trigger these psychiatric disorders. This effect is partly mediated by the hormone corticotropin-releasing factor (CRF), which plays a key role in modulating the autonomic, immune and behavioral effects of all kinds of stress. Increases in CRF are associated with increased symptoms of PTSD and depression.

Is this general model consistent with animal research findings linking early trauma with hypothalamic-pituitary-adrenal (HPA) axis functioning? In a rat model of neglect, rat pups were removed from their mothers for 3 hours daily between the ages of 2–14 days and then returned to their mothers in the animal colony for a week before weaning; this naturalistic stressor is thought to be analogous to neglect in human childhood

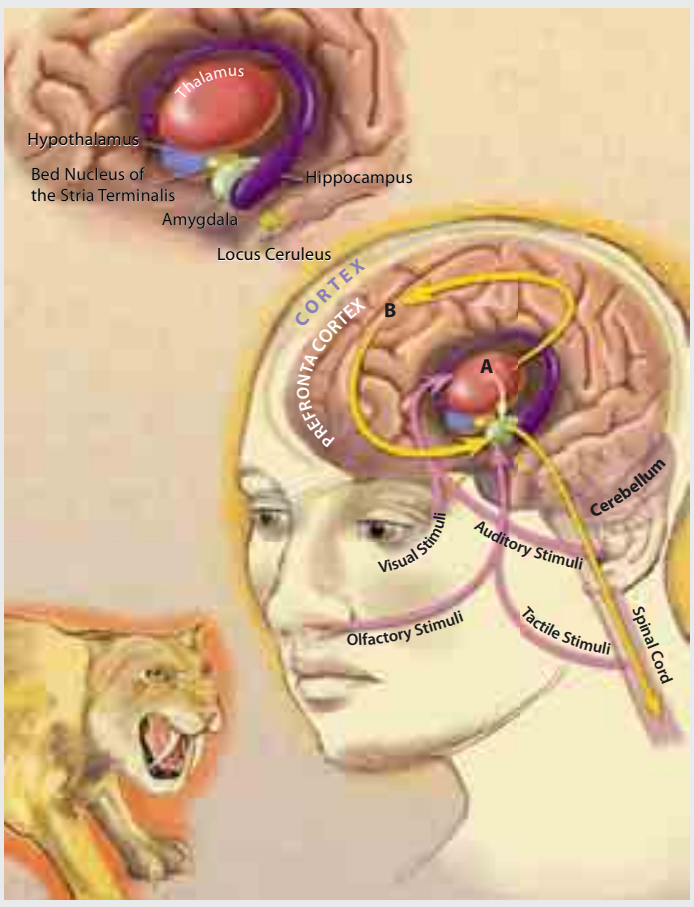


Fig. 1. Body's response to a threat or perceived threat (see box 1 for details). [Reprinted from ref. 8 with permission from Elsevier. After a diagram in the June 10, 2002 issue of *Time* Magazine.]

up to the age of 4–5 years [3]. Researchers found that rat pups subjected to this type of maternal deprivation at the age of 10 days had significant reductions in median eminence CRF concentrations after 24 hours, which can be interpreted as an increase in hypothalamic CRF release. However, the effect was seen only during a critical time window – maternal deprivation did not reduce CRF concentrations in older rat pups.

Can these animal findings on hormone responses to early life trauma be extended to the clinical arena dealing with patients? In a very interesting study, US researchers examined hormone levels (cortisol) of women in the emergency room, immediately after being raped [4]. Three months later, these woman were assessed for PTSD and were interviewed about their histories of trauma. The researchers found that the rape victims who also had a history of childhood sexual abuse were more likely to have PTSD after 3 months. They also found that the women with sexual abuse histories had lower cortisol levels soon after the rape than the women without such histories. This finding supports the idea that chronic trauma results in a distortion of the stress response and in a sensitization towards aggravated stress responses to newly experienced trauma.

Resilience factors

Aversive childhood experiences are certainly not the only known risk factor for PTSD. However, let us turn to the other side of the coin of PTSD development: resilience factors. Resilience toward aversive life events has been addressed since ancient times by authors as diverse as Confucius ("Our greatest glory is not in never falling, but in rising every time we fall") and Nietzsche ("That which does not kill us can only make us stronger").

A wealth of elements that comprise resilience have been proposed in the literature, including active problem-solving, responsibility, self-esteem, independence, well-being, initiative, humor, insight, creativity and many others. Measuring these concepts and understanding their respective roles presents a formidable challenge. One of the recently researched concepts is that of posttraumatic growth, referring to a positive psychological change arising from the struggle with a major life crisis. Only in recent years have positive changes following trauma and adversity been studied systematically. They have been reported empirically following highly stressful events such as severe physical illness, injury, rape and sexual assault, military combat, natural disasters and accidents.

Posttraumatic growth refers to psychological changes that include an identification of new possibilities, more meaningful interpersonal relationships, increased appreciation of life, changed priorities and an increased sense of personal strength and growth in the domain of spiritual and existential matters. It is not yet clear whether posttraumatic growth constitutes a more uniform resilience factor to subsequent PTSD or if it is a more complex phenomenon comprising realistic as well as illusory components [5]. However, it is interesting to study where it may work in the brain, i.e. which brain structures constitute this resilience factor.

Popular brain models suggest that positive emotionality and personal attitudes (e.g. goal-directed approach tendencies: challenging oneself and striving to achieve in the face of adversity) are constituted by left frontal brain activation. In contrast, dominance of right frontal brain activation is related to more negative emotionality and depression. In a study of 82 survivors of traffic accidents with PTSD, our group found that people who had high levels of posttraumatic growth (= positive psychological change marked by an active change of attitudes, goals and personal relations) also had higher levels of left-hemispheric frontal activation, while people who had lower levels of posttraumatic growth had lower activation in that area [6].

Again, a variety of other resilience factors have been formulated and investigated, including those that are constituted by interpersonal or community factors, e.g. having somebody to talk to or being socially supported by others after a trauma. More about such social resilience factors can be found in a recent book by Resick [7].

Neural circuits, memory and body reactions

So far, I have not discussed exactly how a trauma affects the mind and body. How do mind and body react to a sudden, overwhelming threat? The main components of the central nervous system that respond to threats are the thalamus (the gateway for sensory inputs), the hippocampus (which is involved in memory access) and the amygdala. The amygdala drives the initial response to a traumatic event, instigating what is classically known as the "fight or flight response." The clinical course is subsequently modified by memories managed in neural circuits between the hippocampus and the frontal brain (cortex).

Together, these brain structures coordinate how we experience threat and learn to avoid pain. As mentioned above, the amygdala is the primary responding structure. It has a twofold function. It recognizes danger signals rapidly through primitive visual pathways that bypass the cortex, evaluating objects in the environment before interacting with them. It can very quickly activate nearly every bodily system to engage the threat – or flee it. Signals from the amygdala, though, also enhance the processing of fear-inducing information by higher cortical structures, and the amygdala stimulates the hippocampus to help the brain learn and form danger-specific memories. The magnitude and experience of the threat and the subsequent reexperiencing, avoidance/numbing and hyperarousal/hypervigilance are important determinants in the clinical development of PTSD. Figure 1 and box 1 outline how the body responds to a threat.

Thus, initial responses to a traumatic stress are largely biological and driven by the amygdala, while the memories engendered by the hippocampus and the cognitive decisions made by the cortex will organize the mid- and long-term behavior of subjects exposed to traumatic stress. One way to understand PTSD is as a failure to recover from a universal set of immediate emotional and biological reactions to a traumatic stress: memory and adaptive responses malfunction, and with each exposure to a trauma-related stimulus, the subject is once more flooded by immediate-threat responses.

Neurobiological long-term outcomes may be the already described imbalances or distortions of stress hormones of the HPA axis (such as CRF and cortisol) or the persistent asymmetry of brain hemisphere activation in the frontal cortex. My group has been investigating in more depth the manifestations of brain asymmetry in PTSD [9]. Cognitive studies with PTSD sufferers have found that they reexperience symptoms of traumatic events very vividly, and usually visually. These trauma memories are quite different from the remembering of ordinary autobiographical memories, in which sensory elements are integrated into a personal narrative and which seems to be primarily dependent on the left hemisphere.

The study of traffic accident victims has supported these findings: PTSD patients displayed a pattern of increased right-sided activation during exposure to a trauma-related picture when compared with two other groups, traffic accidents survivors without PTSD and healthy, nontraumatized controls. The opposite pattern of relative left hemisphere activation during exposure to the trauma-related picture was observed in traffic accident survivors without PTSD. This latter finding might reflect more adaptive tendencies to process the threat experience by posttraumatic growth (as discussed above).

As mentioned earlier, neurobiological changes involve not only the brain but peripheral body regulation as well. An elevated heart rate has been a prominent marker for PTSD-related hyperarousal in the body. In early research on heart rate at rest (so-called baseline arousal), PTSD patients were found to have a higher resting heart rate than controls – by up to 10 beats per minute – while more recent studies have shown that the heart rate of PTSD patients is particularly elevated when they are being reminded of or are reexperiencing the trauma. Since a chronic heart rate elevation of this magnitude may cause medical complications in later

Box 1. Subcortical and cortical responses to threat

Immediate (subcortical) response to threat (A)

- Upon seeing or hearing a threat, visual and auditory stimuli arrive at the thalamus.
- This information immediately passes from the thalamus to the fear center in the amygdala. Olfactory and tactile stimuli are sent *directly* to the amygdala, bypassing the thalamus; they evoke stronger memories and feelings than do sights and sounds.
- The amygdala alerts other brain structures, including the hypothalamus and locus ceruleus. Somatic responses include sweaty palms, tachycardia, increased blood pressure and a surge in norepinephrine.
- The threatened individual is then prepared for a "fight or flight response."

Cognitive processing of threat (B)

- After fear activation, the thalamus sends information to the cortex for cognitive processing.
- The neocortex analyzes the data from the sensory organs and decides whether or not to continue the fear response.
- If the decision is to maintain the fear response, the amygdala remains on alert and the hippocampus is inhibited in the laying down of event-related memories. The hippocampus is the memory-organizing center of the brain and an important regulator of the stress response.

life, successful treatment of PTSD is needed not only for healing the wounds of the psyche but also such "wounds" of the body.

Treatment works

Two highly positive statements can be made with respect to the treatment of those suffering from trauma. First, we have recourse to several psychotherapeutic techniques that are highly effective for the majority of patients. Second, successful therapies are indeed able to correct the neurobiological distortions consequent to trauma that I have described above.

What is the evidence for the first statement? Although most therapists working with traumatized individuals use psychodynamic or supportive counseling approaches – for which there are no efficacy data – most studies of PTSD treatment outcomes have explored cognitive-behavioral therapy (CBT). CBT for PTSD includes two general subtypes of therapeutic technique. In exposure techniques such as systematic desensitization and flooding, patients confront their fears, object, situation, memories and images without being as overwhelmed as they had anticipated. These experiences of exposure thus serve to disconfirm and correct inner beliefs like "my memories will certainly drive me crazy." Cognitive techniques identify and challenge erroneous cognitions (e.g. "the world is unjust or malevolent," "bad things always happen to me"), aiming to replace them with more realistic cognitions. These procedures can be accompanied by an anxiety management component, which includes a variety of techniques such as relaxation, controlled breathing and self-distraction (thought stopping); patients carry out exercises designed to improve their anxiety management skills.

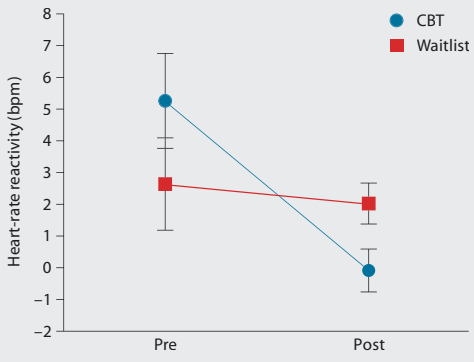


Fig. 2. Mean heart rate reactivity scores for a trauma-related picture in the CBT treatment group and a waiting list control group with no therapy, pre- and posttreatment [with permission from ref. 10]

In detail, particular CBT components for PTSD have been developed from a biopsychological understanding of this disorder. In PTSD, a wide range of psychological processes are disrupted, including attention, beliefs, cognitive-affective responses, memory, styles of coping and social-support systems, all of which need to be appropriately and adequately addressed during the course of treatment.

Box 2.
Eye movement desensitization and reprocessing (EMDR) is an effective combination of body-focused and cognitive-behavioral therapy developed by the psychologist Francine Shapiro in the early 1990s to help alleviate the distress associated with trauma. During EMDR, the client is asked to concentrate on the traumatic experience with its associated negative beliefs and sensations while simultaneously moving his or her eyes back and forth focusing on an external rhythmic stimulus such as hand movements by the therapist or alternating right-left sounds. The patient is then directed to concentrate on a positive thought (something that feels positive and safe), which is reinforced by the EMDR and replaces the negative one. How this actually works is unknown, and there exists some controversy about the necessity for all components of the therapy, especially the eye movements. Nevertheless, EMDR has been used successfully to desensitize anxiety in PTSD patients.

Strict evaluations of these psychotherapies by high-quality methodologies have shown a benefit of psychotherapy for most patients with PTSD. Comprehensive surveys of the available data (so-called metaanalyses) have amalgamated the results from numerous psychotherapy studies conducted between 1980 and 2005 and found that about two-thirds of patients with PTSD completing treatment with various forms of CBT or a new treatment developed specifically for PTSD – eye movement desensitization and reprocessing (EMDR; see box 2) – improve or recover fully.

Treatment studies with CBT or EMDR psychotherapies have also been able to show repair or reconstruction of distorted neurobiological processes in PTSD. When our own clinic treated traffic accident victims with PTSD, we assessed several biological processes before and after treatment. One focus was right-hemispheric activation during exposure to trauma-related pictures. The majority of patients who significantly improved during psychotherapy showed the same brain activity pattern as healthy control persons, namely relative left hemisphere activation during exposure, reflecting a turn to more adaptive tendencies to deal with the traumatic memories. Other research focused on heart rate changes in PTSD. Figure 2 shows a reduction of 5.5 heart beats per minute in those who received CBT. This is an important prophylactic diminution in a chronic cardiovascular handicap that can be triggered by the recall of traumatic experiences.

What, though, about the 30% of patients of all available psychotherapy studies who showed little or no improvement? What strategies might help them? Results on the full range of body and mind changes after trauma imply that instead of going through a single psychotherapy pathway to recovery, different treatment modalities may be able to modulate the system in different ways. Drug treatment of various kinds might act primarily via a subcortical ("bottom-up") approach and psychotherapeutic approaches primarily via a cortical ("top-down") approach. Subtyping PTSD according to the brain's states might also be an effective method for selecting the best treatment modality for a given patient.

Andreas Maercker is Professor of Psychopathology at the Department of Psychology, University of Zürich, and director of a psychotherapeutic outpatient clinic. Trained in medicine and psychology at the universities of Halle and Berlin, he became Professor of Clinical Psychology and Psychotherapy at the University of Dresden in 1999. His research covers both clinical and epidemiological work, focusing on the etio- and pathogenic pathways of mental disorders, with particular interests in PTSD, complicated grief and disorders of the elderly. He has authored and coauthored several books and diagnostic instruments and is associate editor of the Karger journal *Verhaltenstherapie*.

References

1 Mc Cauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, Ryden J, Derogatis LR, Bass EB: Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 1997;277:1362–1368.
2 Maercker A, Michael T, Fehm L, Becker ES, Margraf J: Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. Br J Psychiatry 2004;184:482–487.
3 Pihoker C, Owens MJ, Kuhn CM, Schanberg SM, Nemeroff CB: Maternal separation in neonatal rats elicits activation of the hypothalamic-pituitary-adrenal axis: a putative role for corticotropin-releasing factor. Psychoendocrinology 1993;18:485–493.
4 Resnick H, Yehuda R, Pitman RK, Foy DW: Effect of previous trauma on acute plasma cortisol level following rape. Am J Psychiatry 1995;152:1675–1677.
5 Maercker A, Zöllner T: The Janus face of posttraumatic growth: towards a two component model of posttraumatic growth. Psychol Inquiry 2004; 15:41–48.
6 Rabe S, Zollner T, Maercker A, Karl A: Neural correlates of posttraumatic growth after severe motor vehicle accidents. J Consult Clin Psychol 2006; 74:880–886.
7 Resick P: Stress and Trauma. Philadelphia, Taylor & Francis, 2001.
8 Vieweg WVR, Julius DA, Fernandez A, Beatty-Brooks M, Hettema JM, Pandurangi AK: Posttraumatic stress disorder: clinical features, pathophysiology, and treatment. Am J Med 2006;119:383–390.
9 Rabe S, Beauducel A, Zollner T, Maercker A, Karl A: Regional brain electrical activity in posttraumatic stress disorder after motor vehicle accident. J Abnorm Psychol 2006;115:687–698.
10 Rabe S, Dorfel D, Zollner T, Maercker A, Karl A: Cardiovascular correlates of motor vehicle accident related posttraumatic stress disorder and its successful treatment. Appl Psychophysiol Biofeedback 2006;31:315–330.

Karger Gazette

The Karger Gazette, provided free to the biomedical community, appears once a year, highlighting a specially selected topic in biomedicine.

To subscribe please write to:

S. Karger AG, P.O. Box
CH–4009 Basel, Switzerland
Fax +41 61 306 12 34
Email: gazette@karger.ch

Published by S. Karger AG, Basel
Edited by Dagmar Horn and Anne Blonstein(*ab*)
Design by Erich Gschwind

The Karger Gazette is also available online.

www.karger.com/gazette

Picture credits
Title illustration: created by using part of a painting by Lenz Klotz, collection S. Karger AG.
Illustration p. 11: created by using part of a painting by Franz Anatol Wyss, collection S. Karger AG.
With kind permission of the artists.
Illustration p. 2/3: detail of the etching 'Melancholia I' (1514) by Albrecht Dürer; Staatliche Museen zu Berlin.

Illustrations in this issue are used with permission of the following organizations and companies:
Wellcome Photo Library: D.H. Tuke (p. 3)
Nature Publishing Group: Fig. 4 (p. 8)
Elsevier: Fig. 1 (p. 10)
Wikipedia: T. Sydenham; F.A. Mesmer; M.-F.-X. Bichat; J.-M. Charcot, S. Freud (pp. 2, 3)