Hidden Administration of Drugs

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In placebo-controlled trials, the placebo component of treatments is usually assessed by simulating a therapy through the administration of a dummy treatment (placebo) in order to eliminate the specific effects of the therapy. Recently, a radically different approach to the analysis of placebo responses has been implemented in which placebo responses are assessed without placebo groups. To do this, the placebo (psychological) component is eliminated by conducting hidden (unexpected) administrations of the active treatment. Compelling experimental evidence now shows that when the psychological component is eliminated through the administration of therapies unbeknownst to the patient, the effects of a variety of treatments are significantly reduced. Overall, the experimental data show that the action of different pharmacological agents can be modulated by cognitive and affective factors that can increase or decrease the effects of drugs. This experimental approach is thus a window into the complex interactions between psychology and pharmacodynamics.

Any treatment conducted in routine medical practice has two components: one related to the specific effects of the treatment itself and the other related to the expectation about the therapy that is being administered (**Figure 1a**). The latter represents the placebo response. The placebo component of a treatment is usually studied by simulating a therapy through the administration of a dummy treatment (the placebo) in order to eliminate the specific effects of the therapy itself (**Figure 1b**). This approach is typically used in clinical trials and has shown the underlying biological mechanisms of the placebo response in a variety of medical conditions.[1] In recent years, a radically different approach to the analysis of placebo responses has been implemented in which placebo responses are assessed without placebo groups. This experimental approach entails eliminating the placebo-based psychological component while maintaining the specific effects of the treatment (**Figure 1c**). In order to eliminate the placebo component, the patient is made completely unaware that a medical therapy is being carried out. Then, hidden therapies are compared with open ones. The difference between the hidden and the open treatments represents the placebo component even though no placebo has been given. The importance of this approach resides in the fact that open therapies are expected whereas hidden therapies are unexpected. Therefore, a study of the open–hidden (expected–unexpected) paradigm gives us information regarding the role of complex psychological factors, such as expectations, in the therapeutic outcome.[2]

OPEN–HIDDEN PARADIGM

To compare open therapies, which are carried out according to routine clinical practice, with hidden therapies, which are conducted unbeknownst to the patient, two groups of subjects are needed. The group that receives an open treatment does not pose particular problems, whereas the group that receives the hidden therapy requires methodological and ethical considerations. In fact, subjects must give their informed consent to receive a hidden treatment. Although this is not always easy to carry out because of the inherent lack of awareness during hidden administration, protocols have been developed to overcome this problem.

For example, the subjects who receive a hidden treatment are told that they could receive either a drug or nothing, thus giving their informed consent to both possibilities. When a hidden infusion of a drug is performed, these subjects believe that nothing is being administered. Another approach is an unknown temporal sequence of drug administration. In this case, the subjects know that a medical treatment will be administered, but they do not know when. For example, the patient is in a bed with an intravenous line and the drug might be delivered after 30, 60, or 90 minutes through a preprogrammed infusion machine; however, he or she does not know this temporal sequence. If the drug is truly effective, symptom reduction should be temporally correlated with drug administration.

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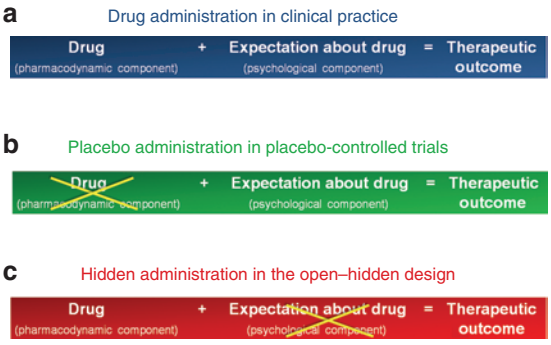

Figure 1 Any pharmacological treatment has a specific pharmacodynamic effect and a placebo psychological component, the latter represented mainly by expectations of clinical improvement. (**a**) In routine clinical practice, the therapeutic outcome is the sum of these two components. (**b**) In placebo-controlled trials, the effectiveness of the drug is assessed by eliminating the pharmacodynamic component through the administration of a placebo. (**c**) In an open–hidden paradigm regimen, the effectiveness of the drug is assessed by eliminating the expectation about the therapy through a hidden (unexpected) drug administration.

Open–hidden administrations

From a practical point of view, it is possible to conduct a hidden infusion of a drug through a computer-controlled infusion pump that is preprogrammed to deliver the drug at the desired time. The essential point is that the patient does not know that any drug is being injected. This hidden procedure is relatively easy to carry out in the postoperative phase; the computer-controlled infusion pump can deliver a painkiller automatically, without a doctor or nurse in the room, and the patient is completely unaware that an analgesic treatment has been started. By contrast, a hidden oral administration is more difficult to carry out because an oral delivery unbeknownst to the patient is surely less practical. Similarly, because many therapies require chronic administration of a drug to achieve clinical efficacy, a hidden administration in chronic conditions is more difficult. For example, the long latency of action of antidepressants makes hidden administration difficult and impractical.

Therefore, there are some limitations in the open–hidden paradigm that are related to the possibility of carrying out a true hidden administration. Another important methodological aspect is represented by the fact that pharmacological agents and doses that induce subjective sensations cannot be given covertly because this sensory feedback makes the subjects realize that a drug has been injected. Consequently, only certain drugs and doses can be tested.

In the 1980s and 1990s, some studies were conducted in which analgesic drugs were administered by machines through hidden infusions.[3–6] For postoperative pain following extraction of the third molar, Levine *et al.*[3] and Levine and Gordon[5] found that the level of pain relief after a hidden injection of a 6–8 mg intravenous dose of morphine corresponded to that after an open intravenous injection of saline solution in full view of the patient (placebo). In other words, telling the patient that a painkiller is being injected (actually a placebo) is as powerful as 6–8 mg of morphine. The investigators concluded that an open injection of morphine in full view of the patient, which represents routine medical practice, is more effective than a hidden one because in the latter the placebo component is absent.

An analysis of the differences between open (expected) and hidden (unexpected) injections of analgesics was carried out by Amanzio *et al.*[7] The effects of four widely used painkillers (buprenorphine, tramadol, ketorolac, and metamizol) in the postoperative setting were analyzed using either open or hidden modes of administrations. A doctor carried out the open administration at the bedside by telling the patient that the injection was a powerful analgesic and that the pain would subside in a few minutes. By contrast, the hidden injection of the same analgesic dose was administered by an automatic infusion machine that started the analgesic infusion without any doctor or nurse in the room. Thus, the patients were completely unaware that an analgesic therapy had been started. The analgesic dose needed to reduce the pain by 50% (AD_{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. Similarly, the time course of postsurgical pain was 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.

Pain is not a special case. Another study was carried out in postoperative patients with high state-anxiety scores on the State-Trait Anxiety Inventory–State (STAI-S) scale.[8] To reduce state anxiety, some of them were treated with open (expected) administrations of diazepam, whereas other patients were given hidden (unexpected) infusions of diazepam (**Figure 2a**). The open and hidden administrations were applied using the same procedures as those described above for pain. The difference between the open and the hidden modes of diazepam administration was highly significant at 2 h after the injection, such that in the open group there was a clear-cut decrease in the STAI-S score, whereas in the hidden group diazepam was totally ineffective.

Open–hidden interruptions

These effects have also been found with hidden interruptions of drug delivery, whereby the administration of a pharmacological agent is interrupted either overtly or covertly. For example, morphine has been studied in detail in this context.[8] The relapse of pain occurs faster and the pain intensity is higher with an open interruption of morphine compared with a hidden one, which indicates that the hidden interruption prolongs the postinterruption analgesia. The faster relapse of pain after the open interruption has been explained as a nocebo effect, in which the knowledge that the therapy has been stopped leads to an increase in anxiety and fear of pain relapse.

Similarly, with respect to diazepam, Benedetti *et al.*[8] showed that in the open condition the STAI-S score increased significantly between 4 and 8 h after interruption, whereas in the hidden condition it did not change (**Figure 2b**). In this case too, the anxiety relapse after the open interruption of diazepam might have been due to the expectation and fear of anxiety relapse in the absence of antianxiety drug administration.

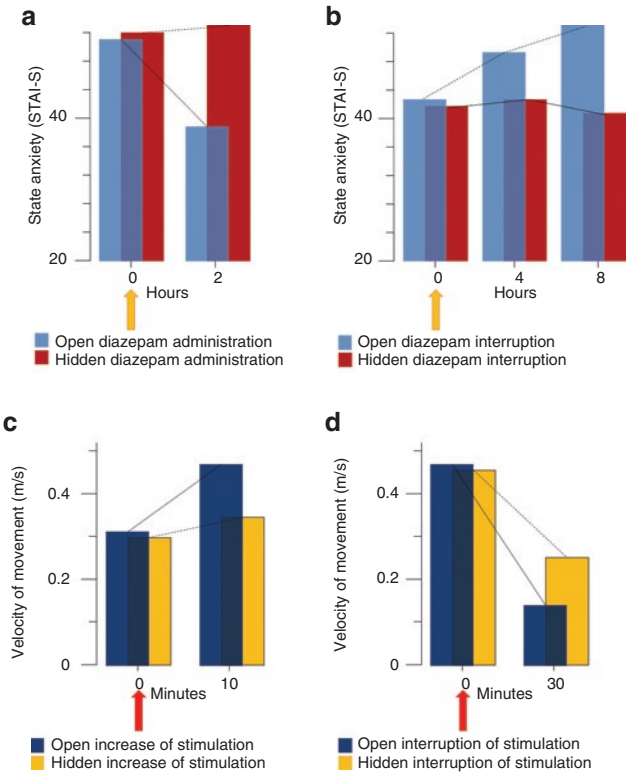

Figure 2 Comparison between open and hidden administrations/interruptions of treatment. (**a**) Decrease in postoperative anxiety 2 h after open and hidden doses of diazepam (10 mg). Note that a hidden injection is completely ineffective in reducing anxiety. (**b**) Anxiety increase 8 h after open and hidden interruption of a diazepam therapy. A hidden interruption does not induce any relapse of anxiety. (**c**) Increase in movement velocity in patients with Parkinson's disease 10 minutes after open and hidden stimulation of the subthalamic nucleus. Note that hidden stimulation is less effective than an open one. (**d**) Decrease in movement velocity 30 minutes after open and hidden interruption of stimulation. Note the smaller decrease after hidden stimulation. STAI-S, State-Trait Anxiety Inventory–State. Data from ref. 8.

Nonpharmacological treatments

The open–hidden paradigm has also been applied to subthalamic nucleus deep-brain stimulation for the treatment of Parkinson's disease. There are at least two lines of evidence indicating that hidden deep-brain stimulation is less effective than open stimulation. The first is provided by studies of stimulation with macroelectrodes in the postoperative phase.[8,9] Using a hand-movement analyzer to assess bradykinesia, Parkinsonian patients carried out a visual directional-choice task in which the right index finger was positioned on a central sensor and was moved toward a target when a light was turned on. Each patient was tested twice, with an overt and covert procedure, on different days. In the open condition, the stimulus intensity was overtly increased to optimal stimulation, along with suggestions of improvement in motor performance (**Figure 2c**). Similarly, the subthalamic stimulus intensity was overtly interrupted, along with suggestions of worsening (**Figure 2d**). By contrast, in the hidden condition, the same procedures were carried out unbeknownst to the patients. The open increase in stimulation was more effective than the hidden one at 10 minutes (**Figure 2c**). Similarly, the open interruption induced a larger reduction of movement velocity at 30 minutes than the hidden one (**Figure 2d**). Therefore, an increase in the hidden stimulus produced smaller therapeutic effects, whereas a hidden unexpected interruption induced a lesser worsening of motor performance.

The second line of evidence that hidden deep-brain stimulation is less effective than open stimulation comes from analysis of autonomic and emotional responses to intraoperative stimulation with microelectrodes.[10,11] Stimulation of the most ventral subthalamic region, which includes the ventral pole of the subthalamic nucleus and the substantia nigra pars reticulata, produces autonomic and emotional responses that are variable over time and vary according to the open or hidden condition of stimulation. In these studies, the minimum stimulus intensity needed to produce a response (i.e., the threshold) increased from 2.25 ± 1.4 V in the open condition to 4.1 ± 0.9 V in the hidden condition. In other words, because a hidden unexpected stimulation is less effective, an increase of the stimulus intensity is necessary to induce an autonomic response.

BRAIN RESPONSES TO OPEN AND HIDDEN TREATMENTS

On the basis of these clinical observations, one of the crucial questions to be answered is related to the mechanisms of brain activity and differences in brain responses between open and hidden treatments. In this regard, the open–hidden paradigm is an excellent model to understand the role of expectations in the therapeutic outcome because the difference between the open (expected) and the hidden (unexpected) treatments is represented by the expectation of the therapeutic outcome. In fact, patients expect a clinical improvement when therapies are given overtly, whereas they do not expect anything when therapies are administered covertly. Although much work remains to be undertaken to understand the mechanisms and the role of expectations in the therapeutic outcome, we are beginning to learn how expectations may enhance the responses to both pharmacological and nonpharmacological treatments, and this knowledge comes from both deep-brain stimulation and brain-imaging studies.

Studies of deep-brain stimulation

During implantation of the electrodes for deep-brain stimulation, both recording and stimulation can be conducted. For example, confirmation of good positioning of the electrode tip in the subthalamic nucleus can be obtained using microstimulation for the assessment of (i) clinical effects, such as reduction of rigidity and disappearance of tremor, and (ii) side effects, such as dyskinesias, muscle contractions, and tingling sensations. Usually, high-frequency (130 Hz) stimulation is used. Therefore, this intraoperative setting represents a good opportunity to use the open–hidden paradigm for deep-brain stimulation. From an experimental point of view, conducting hidden administrations of drugs and then comparing them with open ones is not easy. It requires a computer-controlled infusion pump concealed from the patient's view, and special attention must be paid to the fact that patients must be completely unaware of the treatment being given. Working with a stimulator that can be switched on and off covertly, out of the patient's view, is much easier and hence poses fewer methodological problems.

Stimulation of the subthalamic nucleus, and, in general, of the subthalamic region, has been shown to produce not only motor-related responses but also autonomic responses. Stimulation of the zona incerta by electrical stimuli[12] or glutamate[13] induces cardiovascular responses in rats, and electrical stimulation of the subthalamic nucleus induces a conspicuous increase of heart rate, blood pressure, and respiratory rate in freely moving cats.[14] Similar effects were found in Parkinsonian patients with electrodes implanted in the subthalamic nuclei.[15–17]

A detailed analysis of autonomic responses to intraoperative stimulation of different brain regions has been carried out in Parkinsonian patients during the surgical implantation of electrodes.[10,11] Stimulation of the most dorsal part of the subthalamic region, which includes the zona incerta and the dorsal pole of the subthalamic nucleus, produces autonomic responses that do not differ in the hidden and the open conditions. By contrast, stimulation of the most ventral region, which includes the substantia nigra pars reticulata and the ventral pole of the subthalamic nucleus, produces autonomic responses that vary according to the open or hidden status of stimulation (**Figure 3**). In fact, hidden (unexpected) stimulation is less effective, so an increase of the stimulus intensity is necessary to induce an autonomic response—namely, a change in both heart rate and sympathetic activity, as assessed by heart rate–variability analysis. The stimulus–response curves for the dorsal and ventral subthalamic regions are shown in the inset of **Figure 3**. The neuronal excitability in the hidden condition is reduced only in the ventral part, a region that is involved in associative limbic functions.[18–20] As described above in "Nonpharmacological Treatments," the minimum stimulus intensity needed to produce a response increases from 2.25 ± 1.4 V in the open condition to 4.1 ± 0.9 V in the hidden condition. These data strongly suggest that expectation might increase the excitability of limbic structures such that unexpected stimulations would require an increase in intensity.[11]

Thus, these responses in the subthalamic limbic region appear to be context dependent and are in agreement with previous studies indicating that the particular responses evoked are not related to specific electrode locations but rather to the subject's psychological traits and concerns. In other words, limbic stimulation appears to produce effects that are dependent on the ongoing context.[21] Stimulation of the human subthalamic nucleus has been reported to produce emotion-related responses, such as euphoria and hypomania[22] and mirthful laughter,[23] whereas stimulation of the substantia nigra pars reticulata has been found to induce acute depression.[24,25] The subthalamic nucleus is known to be connected to the ventral pallidum, a major limbic output region,[26] and the temporal lobe is an output target of the basal ganglia.[27] In addition, the activity of the cingulate cortex is modified by high-frequency subthalamic nucleus stimulation.[28] Therefore, the subthalamic region, which includes the zona incerta, the subthalamic nucleus, and the substantia nigra pars reticulata, is a complex area encompassing the motor, associative, limbic, cardiovascular, and autonomic functions.

This region is thus particularly interesting for investigations of an open–hidden design because both subjective emotional responses and objective autonomic responses can be analyzed in some detail. In fact, an open–hidden paradigm was used by Benedetti *et al.*[10] to assess the emotional responses to stimulation of the ventral pole of the subthalamic nucleus. The emotional experiences thus evoked were found to vary across the two different experimental conditions. Some subjects reported no sensations during hidden stimulation (stimulus intensity = 4 V) and no autonomic responses were detected; however, these subjects reported a pleasant sensation during open stimulation of the same locus at the same intensity (4 V), along with detectable autonomic responses. These findings confirm that expectations may increase the excitability of some limbic regions.

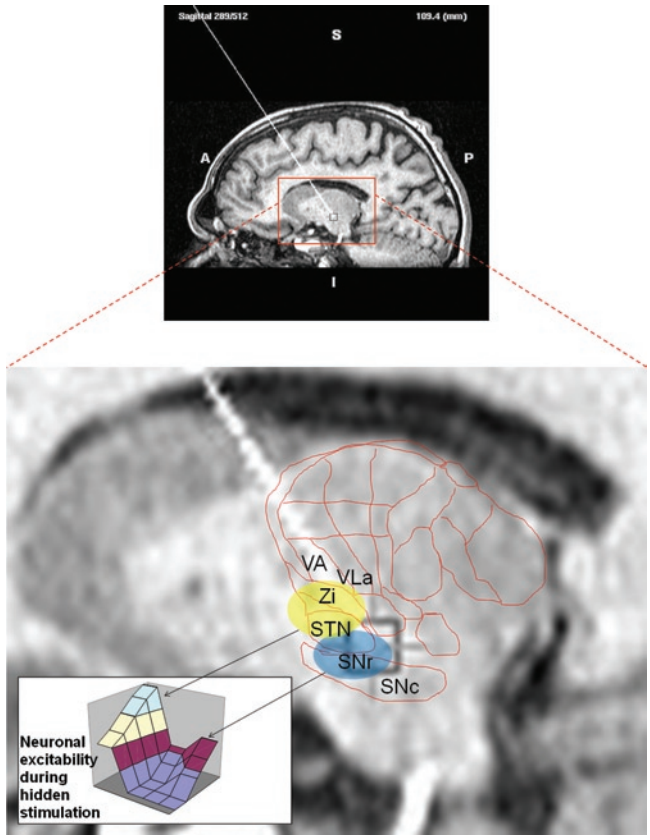

Figure 3 Areas of the subthalamic region where hidden stimulations are less effective than open stimulations (light blue) and areas where there is no difference between hidden and open stimulations (yellow). The light blue area corresponds to the limbic-associative portion of the subthalamic region, whereas the yellow area corresponds to the motor and autonomic control portion. The inset shows the distribution of neuronal excitability, as measured by assessing the threshold of autonomic responses to hidden stimulation. Note that the excitability during hidden stimulation is significantly reduced only in the limbic-associative region. SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventral anterior nucleus of the thalamus; VLa, ventrolateral anterior nucleus of the thalamus; Zi, zona incerta. Data from refs. 10 and 11.

Brain-imaging studies

The fact that expectation may enhance the therapeutic responses by increasing the excitability of some regions of the brain is supported by brain-imaging studies. For example, Volkow *et al.*[29] adopted a balanced placebo design to investigate the effects of

methylphenidate (MP) on glucose metabolism in the brain. Although this study used a balanced placebo design and not an open–hidden paradigm, these two paradigms can be considered similar. In the balanced placebo design, one group expects to receive the drug and indeed receives the drug. A second group expects the drug but receives a placebo. A third group expects a placebo but actually receives the drug. A fourth group expects a placebo and indeed receives a placebo. The first group (told drug, gets drug) is the same as an open-administration group, whereas the third group (told placebo, gets drug) is similar to a hidden-administration group because in the first case the drug is expected, whereas in the third case its administration is not expected.

Using this balanced placebo design, Volkow *et al.*[29] subdivided cocaine abusers into four groups: the first expected to receive MP and indeed received the drug; the second expected MP but received a placebo; the third expected a placebo but actually received MP; and the fourth expected a placebo and indeed received a placebo. The increases in brain glucose metabolism were approximately 50% larger when MP was expected, particularly in the cerebellum and the thalamus, than when it was not (**Figure 4**). By contrast, MP induced larger increases in the left lateral orbitofrontal cortex when it was unexpected compared with when it was expected. In addition, the self-reported "highs" were also 50% greater when MP was expected than when it was not. Volkow *et al.*[29] also found a correlation between the subjectively reported "high" and the metabolic activity in the thalamus; however, this was not the case in the cerebellum. This study indicates that the psychological state of the patient makes a big difference; it can either enhance or reduce the effects of a drug, and the thalamus may mediate this enhancement by expectations, whereas the orbitofrontal cortex mediates the response to the unexpected drug.

The same research group, using the same balanced placebo design, performed a similar experiment in non-drug-abusing subjects who had minimal previous experience with stimulant drugs.[30] MP was found to induce decreases in the striatum that were larger when the subjects expected it than when they did not. In addition, when the subjects expected to receive MP but actually received a placebo, the researchers found increases in the ventral cingulate gyrus and in the nucleus accumbens. The work by Volkow and colleagues[29,30] shows that expectation, and indeed any psychological state, is an important variable to be considered whenever reinforcing and therapeutic effects of drugs are tested both in subjects who consume drugs of abuse and in subjects who have no previous experience of such drugs.

More recently, Bingel *et al.*[31] carried out a functional magnetic resonance imaging (fMRI) study in healthy subjects using an elegant experimental procedure, as shown in **Figure 5** (see also Gollub and Kong, ref. 32). To elicit both positive and negative expectations about how painful a heat stimulus would feel during infusion of the opioid analgesic remifentanil, they first ran a conditioning session in which all participants underwent four sequences of painful heat stimuli. The first two sequences were given during an intravenous infusion of saline, and subjects were told that these were baseline measures in the absence of any

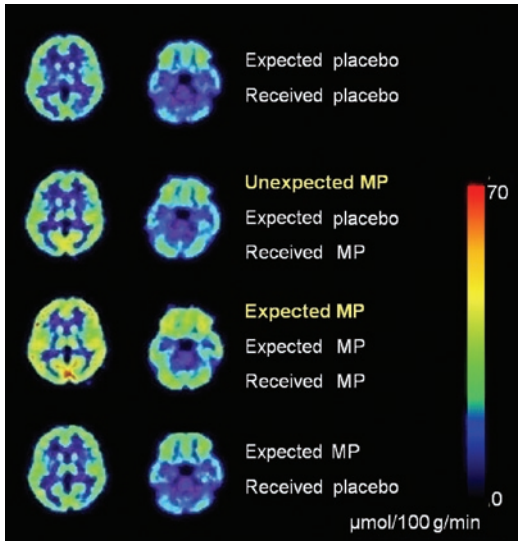

Figure 4 Metabolic images of the brain at the thalamic and cerebellar levels in four conditions: (i) expected placebo, received placebo; (ii) expected placebo, received methylphenidate (MP); (iii) expected MP, received MP; and (iv) expected MP, received placebo. Note the larger increases in metabolism when MP was expected (third panel) than when it was not (second panel). Reprinted from ref. 29 with permission of the Society for Neuroscience, copyright 2003.

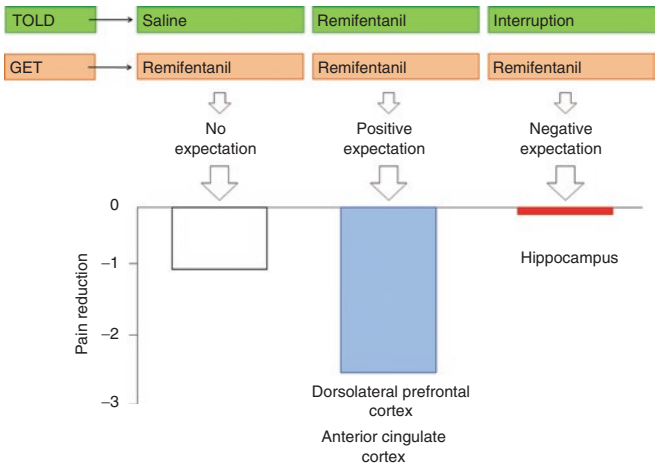

Figure 5 In this experiment by Bingel *et al.*,[31] three conditions are tested. Subjects get remifentanil but are told it is saline; subjects get remifentanil and are told it is remifentanil; and subjects get remifentanil but are told that it has been interrupted. Positive expectations lead to a larger analgesic effect compared with no expectation, along with the activation of several brain regions, such as the dorsolateral prefrontal cortex and the rostral anterior cingulate cortex. By contrast, negative expectations completely abolish the analgesic effect of remifentanil, simultaneously activating the hippocampus.

treatment. In the third sequence, given during an intravenous infusion of remifentanil, the participants were told to expect a powerful analgesic effect, and the temperature of the stimuli was surreptitiously lowered to increase expectations of powerful analgesia. Just before the fourth sequence, the remifentanil infusion was interrupted, the participants were told to expect an increase in pain, and the temperature of the stimuli was surreptitiously raised to increase expectations of hyperalgesia.

In a second session, participants were told that the procedures of the treatment session would be repeated while fMRI scans were performed. Actually, the procedures differed in two ways. First, the remifentanil infusion was started after the first sequence and maintained throughout the remaining three sequences. Second, the temperature of the heat stimulus was kept constant across all four sequences. Therefore, the first sequence represented the baseline, the second the effects of hidden remifentanil (i.e., in the absence of any positive expectation), the third the effects of open remifentanil (i.e., in the presence of positive expectation), and the fourth the effects of hidden remifentanil along with negative expectation. As shown in **Figure 5**, Bingel *et al.*[31] found that when the subjects expected remifentanil (told remifentanil, got remifentanil), they reported less pain than when remifentanil was administered without their knowledge in the hidden condition (told saline, got remifentanil), even though they received identical remifentanil doses and identical noxious stimuli. In addition, during hidden remifentanil administration, when the subjects expected the drug to be interrupted (told interruption, got remifentanil), they reported no pain reduction at all. Most interestingly, fMRI responses showed that different brain networks were activated depending on the direction of the modulation in pain perception (**Figure 5**). Although enhancement of the analgesic effect that accompanied positive expectation was associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex, negative expectation that completely reversed the analgesic effect of remifentanil was associated with increased activity in the hippocampus.

A NATURAL SITUATION OF HIDDEN TREATMENT

Hidden administration of a medical treatment reduces or completely abolishes the efficacy of the treatment. This is due to the absence of patients' expectations about the outcome when a therapy is given covertly (unexpectedly). A natural situation in which expectations are absent is represented by clinical conditions that include cognitive impairment. For example, in Alzheimer's disease, there is an impairment of prefrontal executive control. This executive control has been found to be correlated with specific areas of the prefrontal regions, for example, abstract reasoning with dorsolateral frontal regions and inhibitory control with orbital and medial frontal areas.[33–38] Interestingly, similar regions have been found to be activated by placebo-induced expectation of benefit.[39–42] Alzheimer's disease is known to severely affect the frontal lobes, with neuronal degeneration in areas involved in the analgesic effect of a placebo, for example, the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the anterior cingulate cortex.[43]

Considering all these aspects, administration of open therapies to patients with prefrontal impairment and administration of hidden therapies to nondemented patients should be expected to produce the same effects. In other words, the hidden administration of a therapy to nondemented patients and the normal open administration of a therapy (in full view) to demented patients have a common feature, that is, in both cases there is a lack of awareness about the therapy. In fact, in both cases the patients do not know that a therapy is being administered—in the first case because the therapy is given unbeknownst to the patient and in the second case because there is cognitive impairment. Thus, in both cases, the therapy is unexpected. Reasoning in this way, Benedetti *et al.*[44] studied patients in the initial stages of Alzheimer's disease and after 1 year (see also Colloca *et al.*, ref. 45). They were treated with either open (expected) or hidden (unexpected) local lidocaine to reduce pain following venipuncture, to ascertain whether the expectation component of the therapy, which is represented by the difference between the responses after overt and covert applications, was affected by the disease. In this study, the expectation component of the analgesic therapy was correlated with both cognitive status, as assessed by the Frontal Assessment Battery (FAB), and functional connectivity among different regions of the brain, as assessed by electroencephalographic connectivity analysis (**Figure 6**). In fact, patients with Alzheimer's disease who had reduced FAB scores showed a reduced expectation component of the analgesic treatment. In addition, disruption of the expectation component occurred when reduced connectivity of the prefrontal lobes with the rest of the brain was present. The loss of these expectation-related mechanisms reduced the overall effectiveness of the treatment (lidocaine), and, indeed, an increase of the dose was necessary to produce adequate analgesia.

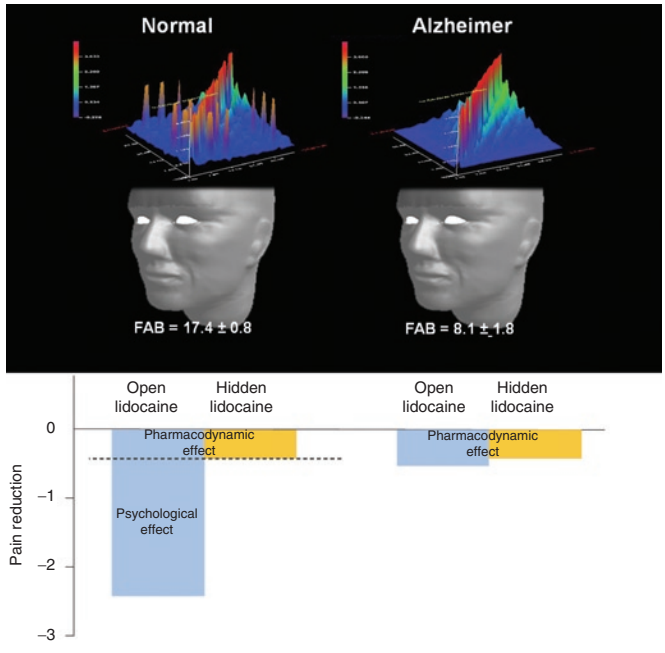

Figure 6 If there is a prefrontal disconnection in patients with Alzheimer's disease, as assessed by an electroencephalographic connectivity analysis (disappearance of the orange peaks in the top panel), in addition to an impairment of the prefrontal executive functions, as assessed by the Frontal Assessment Battery, the open–hidden difference of lidocaine analgesia disappears completely in patients with Alzheimer's disease (right) compared with normal subjects (left). Note that in patients with Alzheimer disease, the psychological (placebo) component is totally abolished. Only the pharmacodynamic component, which is related to hidden administration (free of any psychological contamination), is maintained. In this case, the specific pharmacodynamic effect is very small compared with the psychological effect. Reprinted from refs. 44 and 45 with permission of Springer, copyright 2008.

At least two important clinical implications emerge from the disruption of the expectation mechanism in Alzheimer's disease. First, the reduced efficacy of the open analgesic treatment with lidocaine underscores the need for considering a possible revision of some therapies in Alzheimer's disease in order to compensate for the loss of expectation-related mechanisms. Considering that many patients with the disease are likely to show severe impairment of the prefrontal lobes, and thus a loss of expectation-related mechanisms, low doses of analgesics can be totally inadequate to relieve any type of pain. Therefore, the analgesic treatments should be increased to compensate for the loss of these mechanisms. Second, because the prefrontal cortex can be severely affected in other neurodegenerative conditions, the neuroanatomical localization of expectation-related mechanisms in the prefrontal areas should alert us to the potential disruption of expectation mechanisms in all those conditions in which the prefrontal lobes are involved, for example, vascular dementia, frontotemporal dementia, and any lesion that involves the prefrontal cortex.

COGNITIVE AND AFFECTIVE MODULATION OF DRUG ACTION

Drugs are not injected into a vacuum but into a complex living organism that may be in different states. In particular, human beings continuously switch from one psychological, cognitive, and emotional state to another, and this has been found to affect the global action of a pharmacological agent. As discussed above, one of the best examples of the role of cognitive factors, such as expectations, in the therapeutic outcome is represented by the hidden unexpected administration of drugs. If the patient does not know that a drug is being administered and therefore does not expect any effect, the global action of the drug is reduced. Although hidden administration, which is used mainly in the experimental setting or is present in natural situations such as impairment of the prefrontal lobe, represents an extreme example, numerous studies have shown that the global effect of a drug can be modified, or even reversed, by verbally manipulating the psychological state of the subject. For example, Dworkin *et al.*[46] found that verbal suggestions can change the direction of nitrous oxide action from analgesia to hyperalgesia, with a reduction of both pain threshold and tolerance following electrical stimulation of tooth pulp. Kirk *et al.*[47] found that in drug abusers the response to a drug is more pleasurable when the subjects expect to receive the drug than when they do not. Similarly, Flaten *et al.*[48] showed that carisoprodol, a centrally acting muscle relaxant, resulted in different outcomes, acting either as a relaxant or as a stimulant, depending on the combination of verbal suggestions and drug administration. The same group[49] found that the knowledge that a painkiller was administered caused an increase in the analgesic effect of caffeine, and this increase was due to an interaction of the pharmacological action of the drug and expectancies. The verbal manipulation used in the above-described study by Bingel *et al.*[31] is shown in **Figure 5**.

Thus, the balanced placebo design is an interesting paradigm because it allows the study of cognitive modulation of drug action. As described above,[29,30] this design has been developed to better elucidate the role of suggestion in therapeutic outcome and refers to a methodology for studying the many aspects of both human behavior and effects of drugs, orthogonally manipulating instructions (told drug vs. told placebo) and drug-administration patterns (received drug vs. received placebo).[50] It has been used in many contexts, such as alcohol research[51–54] and studies of the effects of smoking[55] and amphetamine administration.[56]

RELATIONSHIP BETWEEN THE OPEN–HIDDEN PARADIGM AND PLACEBO

The reduction of the global effect of a medical treatment following hidden administration is attributable to the lack of the psychological component of the therapy, of which the most important aspect is likely to be the expectation of the therapeutic outcome. Although other factors, such as the presence of the therapist, may contribute to the overall outcome, the lack of expectation has been the most common factor in the experimental procedure used in most studies. In fact, the main feature of a hidden treatment is that it is unexpected, so that the patient cannot anticipate any therapeutic benefit or clinical improvement. Therefore, the difference between an open and a hidden treatment can be considered the expectation, or placebo, component of the therapy, even though no placebo has been administered. As shown in **Figure 6**, the real pharmacodynamic effect of a drug is represented by its hidden administration, free of any psychological component. The remainder of the observed effect is the psychological effect, or the placebo response.

In this context, the Hawthorne effect is also worth considering, particularly because of its importance in clinical trials. This effect describes the clinical improvement in a group of patients that is attributable to the fact that they know they are being observed. In other words, patients who know that they are being studied may expect a better therapeutic benefit because of the many examinations that they undergo, the special attention they receive from the medical personnel, and their trust in the new therapy under investigation. Therefore, the psychological factors involved in the Hawthorne effect can be eliminated, at least in part, by using a hidden, unexpected therapy.

The recent explosion of placebo research has provided new insights into the neurobiological mechanisms of the placebo response in general, and of expectations in particular. Expectation of the therapeutic benefit triggers a number of neurotransmitters that modulate a variety of symptoms, from pain to motor performance and from anxiety to depression (for a review, see refs. 1,57–63). The model emerging today is that different psychological states and social stimuli induce expectations that activate neurotransmitters and neuromodulators that bind to the same receptors to which drugs bind. Thus, expectations can trigger biochemical pathways that are similar to those activated by pharmacological agents. For example, as shown in **Figure 7**, expectations have been found to activate, among others, opioids in pain[64–66] and dopamine in both Parkinson's disease[67] and pain.[68] Therefore, when a narcotic or an anti-Parkinson agent is administered, interference may occur between

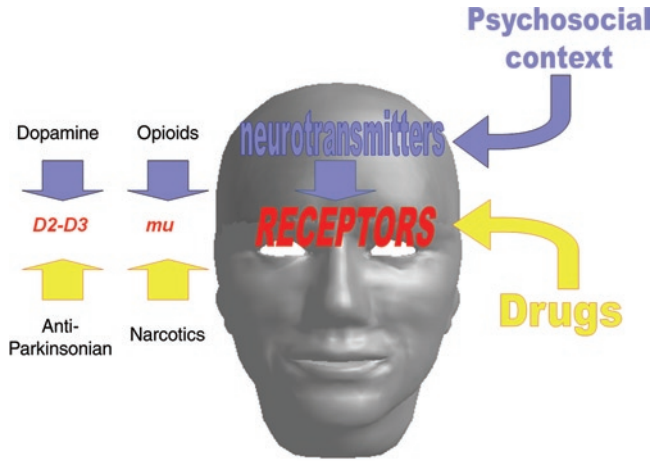

Figure 7 The psychosocial context around the treatment—the ritual of the therapeutic act—activates a variety of neurotransmitters, such as opioids and dopamine, which use the same receptorial pathways that are affected by drugs, thus allowing a cognitive and affective modulation of drug action. The very act of administering a drug may perturb the system and change the response to the drug.

the psychological and the pharmacodynamic factors. In other words, a hidden (unexpected) administration renders all expectation-activated biochemical pathways silent, thus eliminating such interference.

IMPLICATIONS

Clinical trials

The cascade of biochemical events induced by expectations and placebos is likely to interfere with the effects of any drug administered. In other words, drugs are not administered in a vacuum but rather into a complex biochemical environment that varies according to the patient's cognitive/affective state. Any drug that will be eventually given for a specific condition may act on a set of receptors that could have been modified by the therapeutic context, as depicted in **Figure 7**.

For example, if we want to test a new opioid analgesic agent that binds to μ-opioid receptors, a paradoxical situation may occur. When we administer the new opioid agonist, it will activate the μ-opioid receptors. However, the same μ-opioid receptors will be activated by the expectation of analgesia as well. Will the observed analgesic effect be due to the drug-activated μ-opioid receptors or to the expectation-activated μ-opioid receptors? There is no way to answer this question by using the classic clinical trial methodology.

In 1995, Benedetti *et al.*[6] found that the cholecystokinin antagonist proglumide was better than a placebo and that a placebo was better than a no-treatment regimen for relieving postoperative pain. According to the methodology used in classic clinical trials, these results would indicate that proglumide is an effective analgesic that acts on the pain pathways, whereas a placebo reduces pain by inducing expectations of analgesia, thus activating the expectation pathways. However, this conclusion proved erroneous because a hidden injection of proglumide was totally ineffective. In fact, if proglumide had a specific pharmacodynamic effect, there should be no difference between the results of the open and hidden modes of administration. Therefore, the likely interpretation of the mechanism of action of proglumide is that it does not act on the pain pathways at all, but rather on the expectation pathways, thus enhancing the placebo's analgesic response. In other words, proglumide induces a reduction of pain if, and only if, it is associated with a placebo procedure. We now know that proglumide is not a painkiller but that it acts on placebo-activated opioid mechanisms by enhancing the action of endogenous opioids.

Physics has the Heisenberg uncertainty principle, which imposes limits on the precision of a measurement.[69] We can apply a similar principle to the outcomes of clinical trials. As noted by Colloca and Benedetti,[70] in the same way that the uncertainty principle of physics states that a dynamic disturbance is necessarily induced in a system by a measurement, in clinical trials, a dynamic disturbance might be induced in the brain by virtually any type of drug. The very nature of this disturbance is the interference of the injected drug with the expectation pathways, which affects both the outcome measures and the interpretation of the data. Therefore, as in the Heisenberg principle, the disturbance is the cause of the uncertainty. For example, a pharmacological analgesic agent has its own specific pharmacodynamic effect on the pain pathways, but an interference with the expectation mechanisms might occur. We have no *a priori* knowledge of which substances act on the pain pathways and which on the expectation mechanisms. Indeed, virtually all drugs might interfere with the top–down mechanisms; therefore, this uncertainty cannot be solved with the standard clinical trial design. The only way to partially solve this problem is to make the expectation pathways silent. To do this, the treatment must be given covertly (unexpectedly), so that the subject does not have expectations. In this manner, a drug may truly be given—at least in part—in a vacuum, free of any psychologically induced activation of biochemical pathways.

Clearly, if we want to test a new drug for relieving pain, the administration itself may interfere with its real pharmacodynamic effects. On the basis of the above considerations, we can conclude that complex cognitive/affective factors are capable of modulating the action of drugs through activation of the very same receptors to which drugs bind. Therefore, a drug that is tested according to the classic methodology of clinical trials can paradoxically be better than a placebo even though it has no analgesic properties.[6] This leads to an important question. Is the therapy that the doctor administers really effective? Or, does it act through a specific action? Alternatively, does the patient's psychological state modify (by either increasing or reducing) its effects?

As stated above, the only way to partially solve this problem is to make the expectation pathways silent, through a hidden (unexpected) administration, so that the mechanisms activated by expectations are no longer operative. An example of two open–hidden trials showing both an ineffective and an effective treatment is depicted in **Figure 8**.[70] In a clinical trial of this type, the larger the difference is between the effects of the open and hidden administrations, the larger the placebo component and, therefore, the smaller the active effect of the treatment

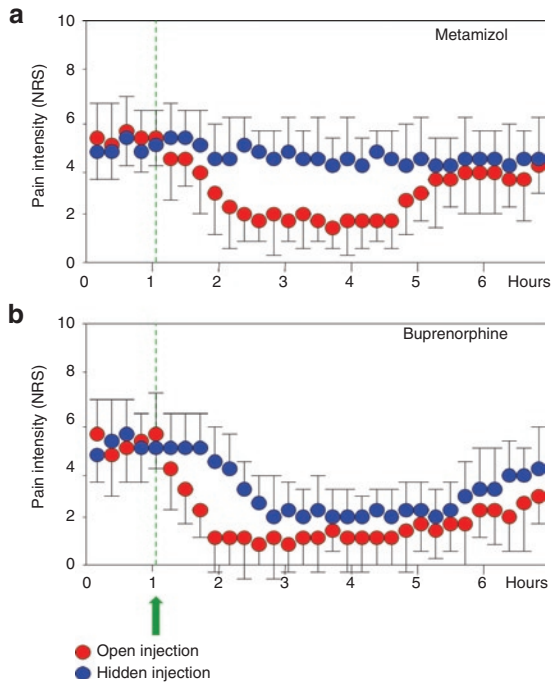

Figure 8 Examples of two clinical trials that used the open–hidden paradigm, showing (**a**) an ineffective and (**b**) an effective treatment. In a clinical trial of this type, the larger the difference is between the effects of the open and hidden modes of administration, the larger the placebo component and, therefore, the smaller the active effect of the treatment being investigated. Conversely, the smaller the difference is, the greater the specific effects of the treatment. In **a**, a 300-mg dose of metamizol is tested in postthymectomy pain. In **b**, a 0.2-mg dose of buprenorphine is tested in postthoracoscopy pain. NRS, Numerical Rating Scale. Reprinted from ref. 70.

being investigated. Conversely, the smaller the difference is, the greater the specific effects of the treatment. In the trial shown in Figure 8a, a 300-mg dose of metamizol was tested in 10 patients to investigate whether it is effective in relieving postthymectomy pain. One group of patients received an open injection of metamizol combined with the information that the pain would soon subside. The patients in the other group knew that metamizol was going to be administered, but they did not know when. To create this condition, a computer-controlled infusion pump was preprogrammed to deliver the drug at the desired time, out of view of the patient. A hidden injection was totally ineffective in reducing pain, which indicates that the positive outcome of the open administration was only a placebo effect. In the other trial, shown in Figure 8b, a 0.2-mg dose of buprenorphine was tested in 12 patients to investigate whether it was effective in relieving postthoracoscopy pain. The figure shows that the difference between the open and hidden conditions was small, which indicates that buprenorphine is an effective analgesic. However, note the slower decrease of pain in the hidden patient group compared with that in the open one, which indicates that most of the initial benefit in the open group was due to a placebo effect.

Clinical practice

These studies show that a patient's knowledge about a therapy affects the therapy outcome. In the open condition, the patient knows the details of the therapy, why it is carried out, and what outcomes to expect. By contrast, in the hidden condition, the patient is completely unaware that a therapy is being given. In this covert situation, no doctors or nurses are present in the room, and the treatment is started by a preprogrammed machine. Although many factors and variables may contribute to the differences between the two situations, certainly the awareness of the treatment, the presence of the therapist, and the expectation of the outcome are likely to play a crucial role. Because all these factors are strongly influenced by the doctor–patient interaction (e.g., the doctor's words), the patient's knowledge about a therapy appears to be fundamental to producing the optimal therapeutic effects. Another important point is the interruption of a therapy. Interestingly, and paradoxically, the awareness of the patient about a treatment is advantageous only while the therapy is being administered. If the therapy must be interrupted, such awareness might be deleterious for the patient. In fact, the open interruption of diazepam or subthalamic stimulation (Figure 2) produces a greater worsening of the symptoms compared to a hidden one. Therefore, the expectation of worsening after interruption of the treatment may counteract the beneficial effects that are already present.

In clinical practice, all efforts should be made to make the patient aware of what is going on, why a procedure is carried out, and what type of outcome should be expected. As described above, this is well evident in patients with Alzheimer's disease who have impaired prefrontal connectivity, in whom the expectation component of the treatment is lost and the global effect of analgesics is reduced. The differences in the outcomes between open and hidden administrations of therapies should induce doctors, nurses, psychologists, and all other medical and paramedical personnel to increase their interactions with patients.[71] Even when a treatment must be stopped, what the therapist tells the patient is essential. The manner in which drugs and brain stimulation are delivered or interrupted plays an important role in the therapeutic outcome.

FUTURE DIRECTIONS

What we need to understand today is where, when, and how expectations work across different medical conditions and therapeutic interventions. In particular, we need to better characterize the neuropharmacology and the neuroanatomy of both expectation and placebo responses in order to understand their possible interactions with the pharmacological agents that are administered in routine clinical practice. More specifically, we will need to determine whether modulation of expectation alters the fundamental drug–receptor interaction. In fact, the studies discussed in this article do not prove this result; rather, they indicate that the cognitive influence of expectation is sufficient to provide an additional (add-on) benefit or to completely mask (cover up) the real effects of the drug. Therefore, future research needs to prove that direct influences of expectation do, in fact, occur at the level of drug–receptor interactions. This new knowledge will be of paramount importance both in the clinical trial setting and in medical practice because it will give us insights into the complex interaction between the psychological states of the patients and their responses to different therapeutic agents.

It should also be pointed out that the open–hidden paradigm, because of the limitations described at the beginning of this article (e.g., oral and chronic administration of drugs), cannot replace the classic clinical trial approach. Nevertheless, it represents a useful tool in the hands of neuroscientists to understand how our brain works and how it can modulate drug action.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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