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Expectation enhances autonomic responses to stimulation of the human subthalamic limbic region ☆

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Abstract

Recent studies show that the placebo component of a treatment can be investigated by administering therapies either overtly or covertly, without the administration of any placebo. Here, we analyze the effects of open (i.e., expected) versus hidden (i.e., unexpected) stimulations of the human subthalamic region on autonomic responses in Parkinson patients. To do this, we mapped the whole subthalamic region, from the dorsal to the ventral part, and recorded both heart rate and sympathetic responses by using spectral analysis of heart rate variability. We found that open stimulations were more effective than hidden ones only in the ventral subthalamic region, whereas no difference between the two conditions was found in the dorsal aspect. By analyzing the stimulus–response curves in the dorsal, middle, and ventral subthalamic regions, we found that the autonomic response threshold was higher in the hidden than open condition for both heart rate and sympathetic responses only in the ventral part. As this ventralmost portion of the subthalamic region is involved in associative-limbic functions, these data suggest that expectation enhances autonomic responses only if these are elicited in the limbic system. These results extend previous findings on the open–hidden paradigm in deep brain stimulation [Benedetti, F., Colloca, L., Lanotte, M., Bergamasco, B., Torre, E., Lopiano, L., 2004a. Autonomic and emotional responses to open and hidden stimulations of the human subthalamic region. Brain Res. Bull. 63, 203–211.], and indicate that expectation plays a major role in the therapeutic outcome. In light of the interactions between the sympathetic adrenergic system and the immune system, the open–hidden difference in autonomic responses might be relevant to the understanding of how expectations might affect the immune system.

Keywords: Expectation; Placebo; Deep brain stimulation; Subthalamic region; Parkinson's disease; Autonomic nervous system

1. Introduction

Expectation of an outcome plays a major role in the placebo response (Amanzio and Benedetti, 1999; Benedetti et al., 1999, 2003b; Colloca and Benedetti, 2005). The recent introduction in biomedical research of the open–hidden paradigm allows the investigation of both expected and unexpected therapeutic outcomes and the identification of the placebo effect without the administration of any placebo (Colloca et al., 2004). An open treatment is performed in full view of the patient who knows what is going on and expects an outcome. By contrast, a hidden treatment is performed covertly, with the patient completely unaware that a therapy is being administered, so that he/she does not expect anything. The difference between the open and the hidden treatments represents the placebo, or psychological, component that comes from the patient's expectations and perception of receiving a therapy. It has been shown that open administrations are more effective than hidden

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administrations in many conditions, which indicates that the knowledge about a treatment affects the therapeutic outcome (for a review, see Colloca et al., 2004).

Although most of the studies with the open–hidden approach have used overt and covert infusions of drugs (Amanzio et al., 2001; Gracely et al., 1983; Levine and Gordon, 1984; Levine et al., 1981), recently intraoperative overt and covert stimulations in awake humans have been investigated (Benedetti et al., 2004a). For example, it has been shown that the open stimulation of the limbic portion of the subthalamic region is more effective in eliciting both autonomic and emotional responses than the hidden stimulation. In addition, by analyzing the thresholds for inducing autonomic responses, an increase in threshold in the hidden condition was found, suggesting that overt stimulation has a facilitating effect on the autonomic responses, probably through the involvement of expectation and anticipation mechanisms (Benedetti et al., 2004a). In previous studies, it has also been shown that the effects of subthalamic nucleus (STN) stimulation can be modulated by complex psychological factors. In fact, context-related cues, like verbal suggestions, can produce different outcomes following STN stimulation (Benedetti et al., 2003a,b; Pollo et al., 2002). Context-related cues and placebo administration have also been shown to induce a release of dopamine in the striatum (de la Fuente-Fernandez et al., 2001) and a change of neuronal activity of the STN of Parkinsonian patients (Benedetti et al., 2004b), thus suggesting that the entire basal ganglia circuitry can be affected by psychological manipulation.

On the basis of these considerations and of our previous study on the open–hidden stimulation of the subthalamic region (Benedetti et al., 2004a), in the present work we performed a detailed analysis of the autonomic responses (heart rate and sympathetic activity) to stimulation of the subthalamic region, to better understand when and where a significant difference between overt and covert stimulations occurs. In light of the close interaction among psychosocial context, autonomic nervous system, and immune system (Bierhaus et al., 2003), the open–hidden difference in autonomic responses might be relevant to the understanding of how expectations might affect the immune system.

2. Methods

2.1. Subjects

Twenty patients participated in the study after they signed a written informed consent for both surgery and mapping procedures. All the experimental procedures were carried out in accordance with the Declaration of Helsinki. The patients were diagnosed with idiopathic Parkinson's disease. Clinical evaluation was performed by means of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987) and the Hoehn and Yahr's (1967) five stages of the disease. Table 1 shows the characteristics of each patient, the UPDRS scores before the surgical implantation of the electrodes, and the duration of the disease, as well as the drug therapy before surgery. All drugs were interrupted the day before surgery.

Table 1
Characteristics of the subjects

Patient	Age (years)	Sex	Duration of Parkinson's disease (years)	UPDRS before surgery	Therapy before surgery
1	57	f	14	60.5	s, pe
2	70	f	20	50.5	m, s, ca, apo, ama
3	53	f	15	39	m, cl, b
4	54	f	14	58	m, ami, ama
5	65	m	22	68	m, ro, v
6	53	m	11	44	s, q
7	65	f	20	65.5	m, pr, d, ci, re, ama
8	66	f	14	70	m, pe, ama
9	68	m	10	58.5	m, pe, b,
10	67	f	16	45.5	s, pr, q
11	50	m	12	56.5	s, pe
12	69	m	24	59	m, s, ca, apo
13	58	f	19	48.5	m, cl, b
14	64	f	10	58	m, ama, cl
15	55	f	17	71.5	m, pe, ama
16	56	m	15	47.5	s, q
17	69	f	17	65	m, pr, ci, re, ama
18	70	m	14	63	m, pe, ama
19	59	f	11	51.5	m, pe, b
20	67	f	20	48	s, q

ama, amantadine; ami, amitriptiline; apo, apomorphine; b, bromazepam; ca, cabergoline; ci, citalopram; cl, clozapine; d, diazepam; m, madopar; pe, pergolide; pr, pramipexol; q, quetiapine; re, reboxetine; ro, ropinirol; s, sinemet; v, venlafaxine.