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No Increased Suggestibility to Placebo in Functional Neurological Disorder

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Abstract

Background: On the basis of occasional strong placebo responses, increased susceptibility to placebo has been proposed as a characteristic of functional neurological disorder. The aim of this study was to clarify whether people with functional neurological disorder have a stronger placebo analgesic response than healthy controls.

Methods: A classic placebo paradigm, with additional conditioning and open-label components, was performed in 30 patients with a functional neurological disorder, and in 30 healthy controls. Ratings of mildly to moderately painful electrotactile stimuli were compared before and after the application of a placebo "anaesthetic" cream versus a control cream, after an additional conditioning exposure, and after full disclosure (open-label component).

Results: Pain intensity ratings at the placebo compared to the control site were similarly reduced in both groups. The conditioning exposure had no additional effect. After placebo disclosure a residual analgesic effect remained.

Conclusion: Functional neurological disorder patients did not have stronger placebo responses than healthy controls. The notion of generally increased suggestibility or increased suggestibility to placebo in FND seems mistaken. Instead, occasional dramatic placebo responses may occur because functional symptoms are inherently more changeable than those due to organic disease.

Introduction

The proposed link between functional neurological disorder (FND) and suggestibility dates back over a century (1,2). Suggestibility is a broad term, encompassing different types. Hypnotic suggestibility has been found to be increased in FND (3), but not interrogative suggestibility (4), nor generalised suggestibility (5). A recent meta-analysis, primarily involving hypnosis and functional seizure induction, identified increased responsiveness to verbal suggestion in FND, but with higher symptom-specific than general suggestibility (6). Thus, are people with FND more suggestible in general or is there an alternative explanation for apparent increased symptom specific suggestibility, such as attentional mechanisms?

A paradigmatic example of suggestibility is the placebo effect. Dramatic placebo responses occur occasionally in FND and like suggestibility feature in most FND definitions (7–11). Does this signify increased suggestibility to placebo, or is it is the illness´ nature that allows placebo responses to manifest as dramatic changes in symptoms?

General susceptibility to placebo has not been tested explicitly in FND. We deliberately chose placebo analgesia, a phenomenon independent of participants' functional symptoms, to allow direct comparison to healthy controls and clarify whether there is generally increased suggestibility to placebo in FND. We hypothesised a normal placebo response magnitude.

Methods

Participants

Thirty-two patients with FND, primarily recruited from our clinical practice, and 31 healthy controls participated. The latter were patients´ family members, acquaintances, and healthy volunteers recruited from University College London's registries and were screened by a neurologist (ACH) for neurological disorders. Participants were told that the study aimed to compare the anaesthetic cream's efficacy between the groups. The information sheet stated that a placebo might be used. Two patients who said they strongly suspected a placebo during debriefing, and one control participant, who reported not having attended to the instructions, were excluded. In the remaining sixty participants, gender and age were matched [17 females in both groups, FND *M*=47.1y, *SD*=16.2, range 21-79y, healthy controls *M*=43.7y, *SD*=12.5, range 21-79y, (t-test $t(58)=-0.91$, $p=.37$]. The FND diagnoses were predominantly functional movement disorders [tremor (23), weakness (7), dystonia (6), gait disorder (6), myoclonus (2), stiffness (2)], chronic pain (5), non-epileptic attack disorder (4), episodic sensory disorders (2), concentration difficulties (1) and foreign accent syndrome (1). Twenty-one patients had multiple FND diagnoses. Nine patients (27%) took daily analgesics, including opioids in four. Two control subjects (7%) took antidepressants.

Experimental setup

Electrotactile stimuli (single 200μs biphasic electric pulses: Digitimer® DS8R, Welwyn Garden City, UK) were applied to the asymptomatic / less symptomatic medial and lateral forearm. Nobody had any pain or sensory symptoms in the tested arm. A verbal countdown preceded all stimuli. First, intensities that were equally mildly/moderately painful (~3/10) were established at both stimulation sites. Subsequently, the "placebo" and the "control" sites were randomly allocated, thereby varying between participants which site was tested first in each condition. Participants rated their perceived pain intensity on a scale from 0 (none) to 10 (worst imaginable) three times at each site for the following conditions:

1. *Baseline*

2. *Post-cream*: after an "anaesthetic" cream had been applied to the placebo site and a face-cream to the control site for ten minutes. In reality, both creams were the same inert face-cream.
3. *Post-conditioning*: Participants were told that the "anaesthetic" cream would be given another five minutes to penetrate deeper and take its effect; a single stimulus would then be given to check if a longer wait was necessary. The usual intensity was administered at the control site, but, unknown to the participant, only half the usual intensity was administered at the placebo site. This conditioning exposure was designed to reinforce the belief that the "anaesthetic" cream was effective. Subsequently the usual stimulus intensities were rated.
4. *Post-disclosure*: The experimenter disclosed that the "anaesthetic" cream was inert. She explained that deceptive placebo is prohibited in clinical practice, but that studies suggest that open-label placebos can be similarly effective and that the next rating shared some properties with open-label placebo. Finally, participants rated the stimuli again.

Results

Mixed-model ANOVAs were performed, with group (FND, healthy control) as between-subject factor, and site (placebo, control) and sometimes also condition (baseline, post-cream, post-conditioning, post-disclosure) as within-subject factors. The assumptions of normality, equality of variance and sphericity were always met.

Baseline: A two-way mixed-model ANOVA of the baseline pain ratings did not show any significant difference between the sites ($F(1,58)=2.27$, $p=.14$, $\eta_p^2=.038$), nor the groups ($F(1,58)=0.88$, $p=.35$, $\eta_p^2=.015$), nor was there any significant interaction between them ($F(1,58)=0.25$, $p=.62$, $\eta_p^2=.004$) (Table 1).

Table 1: Pain ratings in the different conditions

Group average pain ratings on a scale from 0 to 10 at the placebo and the control site for the four different conditions (standard deviations in brackets). For each participant at each site, the stimulus intensity across the four conditions was identical.

Part of the decrease in pain ratings can be attributed to adaptation to the painful stimuli over time, as is apparent on the control site (Table 1). Plotting the difference between the control and placebo sites removes this adaptation component (Figure 1).

Figure 1: Differences in pain ratings between the placebo and control sites

For each condition, the pain rating at the control site is subtracted from the pain rating at the placebo site. A negative difference indicates a placebo effect. The error bars show the standard error of the mean.

Post-cream versus baseline condition: The placebo cream lead to a significant decrease in pain with a large effect size (three-way mixed-model ANOVA, site x condition interaction: $F(1,58)=16.86$, $p=.0001$, $\eta_p^2=.23$), and a trend for this effect to be smaller in the FND group with a medium effect size (group x site x condition interaction: $F(1,58)=3.33$, $p=.073$, $\eta_p^2=.054$).

Post-conditioning versus post-cream: The additional wait and the conditioning stimulus did not significantly decrease the pain rating further than the placebo cream on its own (site x condition interaction: $F(1,58)=0.50$, $p=.48$, $\eta_p^2=.0085$). There was no significant difference in this effect between the groups (group x site x condition interaction: $F(1,58)=0.38$, $p=.54$, $\eta_p^2=.0064$).

Post-disclosure versus post-conditioning: Disclosing that the cream was a placebo lead to a significant increase in pain ratings on the placebo site with a large effect size (site x condition: $F(1,58)=14.54$, $p=.0003$, $\eta_p^2=.20$), but no group x site x condition effect ($F(1,58)=0.16$, $p=.69$, $\eta_p^2=.0028$).

Baseline versus post-disclosure: Comparing pain ratings at baseline to after disclosure, there was a significant site x condition interaction with a medium effect size ($F(1,58)=5.32$, $p=.025$, $\eta_p^2=.084$), but no group x site x condition effect ($F(1,58)=1.90$, $p=.17$, $\eta_p^2=.032$).

Conclusion

Placebo anaesthetic cream induced a placebo effect in both healthy controls and people with FND. Contrary to the notion of generalised suggestibility in people with FND, the placebo response was not larger in the FND group.

Placebo responses per se are not unique to FND, as the placebo arm of virtually any double-blind randomised controlled trial demonstrates. The question is therefore not how placebo responses occur in FND, but how dramatic placebo responses can be explained if not through increased suggestibility. First, structural or biochemical abnormalities impose limits to the placebo effect magnitude in organic disease. Compare stroke-induced to functional hemiplegia. Functional symptoms do not have this "organic limit", thus being able to manifest with greater clinical effects. Second, functional symptoms are inherently more changeable than organic symptoms, exemplified by symptom fluctuations and by improvement with distraction. Third, it is proposed that in FND, there is no abnormality in the basic aspects of movement, perception or cognitive function. Rather, normal basic functioning is suppressed by abnormal higher-level processes (e.g. predictions/attention) (12). Modulation of these higher-level processes by a placebo effect of a "normal" magnitude could manifest as dramatic changes in symptoms.

A further characteristic leading to the interpretation of hypersuggestibility is the exacerbation of functional symptoms when they are discussed. We argue that increased suggestibility might be the wrong interpretation of functional symptom exacerbations. Instead, exacerbations can be explained by attentional focus: functional symptoms manifest with attention and improve/disappear with distraction. Discussing symptoms or triggers directs attention onto them thereby exacerbating them. Although suggestibility to different modalities, e.g. movement disorders or seizures, may differ from suggestibility to placebo analgesia, attentional effects can confound suggestibility studies and lead to erroneous interpretations of hypersuggestibility. Indeed it may partly explain the aforementioned increased symptom-specific rather than generalised hypersuggestibility (6,13). Thus, future suggestibility studies should exclude participants experiencing modality-specific symptoms.

Particular care needs to be taken with terminology, given the stigma and negative attitudes surrounding FND (14,15). “Suggestibility” can have pejorative connotations, implying gullibility or being easily tricked. In fact, larger placebo responses tend even to be associated with desirable traits, such as optimism, ego-resilience, agreeableness and altruism (16,17).

A further finding is that after disclosure, a small but significant placebo effect remained. This was only an approximation to classic open-label placebo, since it followed the experience of deceptive placebo, a conditioning exposure and their disclosure. Further studies are required, but our findings suggest that open-label placebo may be an ethically acceptable supplementary treatment in some patients (18).

Pain ratings were not significantly different between the groups, even after removal of confounders (stimulus intensities, medication, sensory/chronic pain syndromes), thus differing to previous publications (data/analyses available on request) (19).

Study limitations include lack of an organic control group to account for confounds such as differing analgesic use. However, each participant served as their own control, mitigating this effect. Furthermore, repeating the analyses after excluding the nine FND patients and two controls on regular medication that could affect pain perception (analgesics, antidepressants and antiepileptics) gave the same conclusions (all significant and nonsignificant results, including the effect sizes, remained; the trend towards a decreased placebo effect in the FND group disappeared.)

In summary, we found no evidence for stronger placebo analgesia in FND than in healthy controls. The notion that FND patients are hypersuggestible to placebo or in general should therefore be challenged.

Ethics

The study was approved by the London-Bromley Research Ethics Committee (16/LO/1463) and carried out in accordance with the Declaration of Helsinki (20). Participants gave their written, informed consent.

Authorship

Anne-Catherine Huys: conceptualisation, methodology, software, formal analysis, investigation, resources, funding acquisition, data curation, writing – original draft and final version, visualisation.

Brianna Beck: methodology, resources, review and editing.

Patrick Haggard: formal analysis, resources, review and editing, supervision.

Kailash Bhatia: resources, review and editing, supervision.

Mark Edwards: methodology, resources, review and editing, supervision.

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Conflict of interest statement

None of the authors have any financial disclosures / conflicts of interests to declare in relation to this article.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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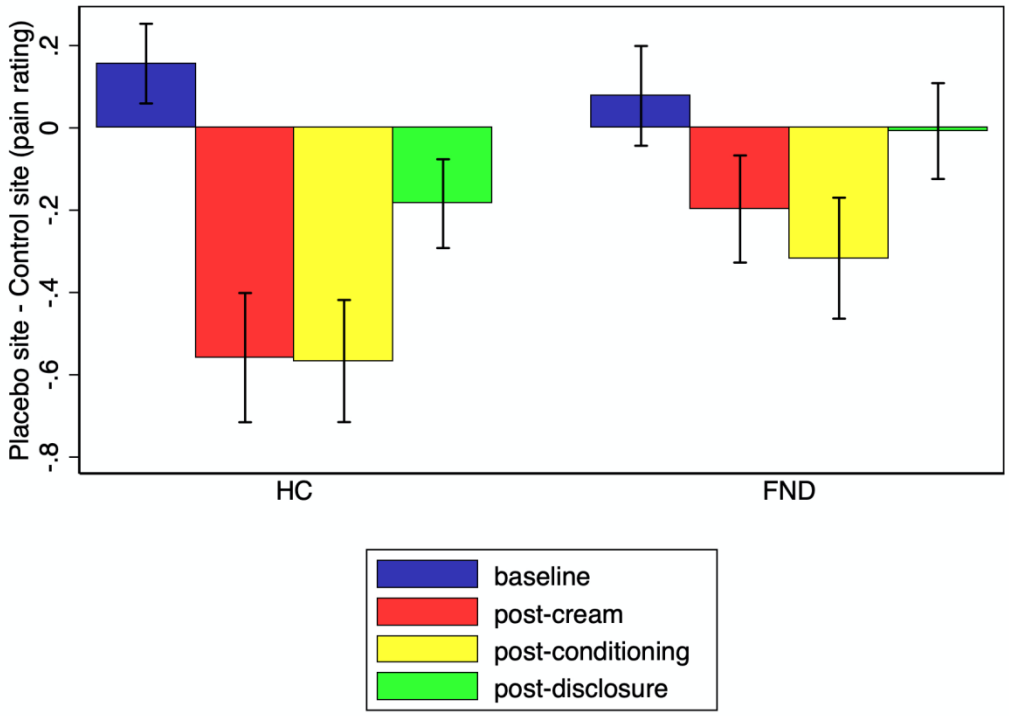
	FND (n=30)		Healthy Controls (n=30)	
	Placebo	**Control**	**Placebo**	**Control**
Baseline (*sd*)	2.83 (1.32)	2.75 (1.31)	3.21 (1.62)	3.06 (1.48)
Post-cream (*sd*)	2.44 (1.37)	2.63 (1.51)	2.62 (1.40)	3.18 (1.72)
Post-conditioning (*sd*)	2.19 (1.38)	2.51 (1.34)	2.32 (1.40)	2.88 (1.61)
Post-disclosure (*sd*)	2.45 (1.48)	2.46 (1.37)	2.66 (1.45)	2.85 (1.59)



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