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The Power of a Good Word: Enhancing the Efficacy of Analgesics in Clinical Settings

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Abstract
Introduction: Communication between medical staff and patients about treatment efficacy elicits expectations of benefit and improves treatment outcomes. While demonstrated in multiple studies via different research methodologies, uniform communication protocols have not been adopted in clinical practice. Here, we summarize the results of two sister studies aimed at bridging this gap. ***Methods:*** Women undergoing C-section (study 1, randomized controlled trial) and patients undergoing general or otolaryngologic surgeries (study 2, control group design) were recruited and assigned to the "regular communication" (RC) or "enhanced communication" (EC) arms. The EC arm received positive information about treatment, while the RC arm received no such information. In both studies, the primary outcome was change in pain intensity; in study 2, an additional outcome was morphine consumption. ***Results:*** Eighty women successfully completed study 1, and 102 patients successfully completed study 2. In both studies, significant time*group interactions were observed ($p < 0.001$). The analgesic effect was virtually twice as large in the EC arm compared to the RC arm. In study 2, in the last two timepoints of assessment, participants in the EC arm also consumed fewer doses of opioids than participants in the RC arm ($p < 0.001$). No significant differences were found in vital signs. ***Conclusions:*** We provide ecological evidence that positive information about treatment significantly decreases pain and opioid consumption during routine clinical care. This study and others could encourage healthcare providers to harness the powerful effects of patients' expectations of benefit to improve analgesics outcomes and, potentially, the outcomes of other symptoms.

Introduction

According to the additive model, the response to any given treatment is the sum of two effects: the underlying mechanism of the active treatment and the placebo response [1, 2]. An alternative, interactive model suggests

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that treatments and placebo responses interact and are not simply additive [1]. Various models notwithstanding the classical placebo theorem assert that the placebo effect stems mainly from patients' expectations of benefit [3, 4], which could derive from conditioning, verbal suggestion, subtle cues, and other contextual elements [4–8].

Extensive research on the analgesic placebo effect, mostly using experimental noxious paradigms in healthy individuals [9–15] and chronic pain patients [11, 12, 15–18], demonstrated large effects. Clinical pain is also heavily subject to the placebo response, which could account for about half of the response to effective analgesic treatments [19–25]. Other creative studies demonstrated large effect sizes when patients received information about the study drug [20, 21, 26–29] but not as part of routine clinical care.

Given that a significant portion of the analgesic response derives from the placebo effect, which could be enhanced by verbal suggestion, it is unclear why verbal suggestion has not been widely adopted in clinical practice. A possible explanation is the literature's lack of direct evidence for the added value of enhancing patients' expectations of benefit from analgesic treatments widely used in routine clinical care [30, 31].

Studies addressing these gaps are rare. A few demonstrated that the large effect of verbal suggestion on clinical pain could be clinically informative. However, those studies investigated clinical pain that does not represent a real clinical challenge, such as pain induced by injection [32] and for which the treatments are not part of routine analgesic clinical care [33].

In this study, we aimed to address this challenge by assessing the effects of a uniform verbal suggestion protocol during analgesic administration in a real-life clinical setting of acute postoperative pain. To this end, we conducted two studies: (1) randomized controlled trial, including women after C-section; and (2) a controlled group design, including participants recovering from general and otolaryngology surgeries.

Methods

Participants

In study 1, women scheduled for C-section in the maternal and newborn department at Carmel Hospital (Haifa, Israel) were invited to participate. In study 2, patients scheduled for general or otolaryngology surgery, under general anesthesia at the Ziv Medical Centre (Zafed, Israel), were invited to participate. Information about inclusion and exclusion criteria, power analyses, patients' recruitment, and nurses' involvement in the studies are found in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541810).

Study Medications

In each study, participants received the same pharmacological treatment (see online suppl. material), given as part of the routine analgesic protocol.

Study Intervention

The study intervention was the verbal suggestion communicated during treatment administration. In the "regular communication" (RC) arms, nurses applied the standard care protocol without any specific verbal instructions. In the "enhanced communication" (EC) arms, patients received positive information regarding the efficacy of the analgesic being administered. See online supplementary material for details on both studies' verbal suggestions.

Main Outcomes

The primary endpoint in both studies was change in patients' self-reported current pain intensity between the first and last assessment, on a 0–10 numerical pain scale (NPS): 0 ("no pain") to 10 ("worst imaginable pain"). In study 1, pain was assessed at baseline (immediately before medication administration) and 1 h after analgesic administration. In study 2, pain intensity was assessed four times, every 10 min, beginning when participants regained consciousness. Those assessment times were chosen because they are part of routine clinical care protocol. For more information about the studies' outcomes, see online supplementary material.

Study Design

Data were collected between March and September 2023 (study 1) and between June 2023 and February 2024 (study 2). Both study teams, located in separate hospitals, were unaware of the details or aims of the other study. For more information about the studies' designs, see online supplementary material.

Statistical Analyses

Statistical analyses were conducted using the SPSS Statistical Package for the Social Sciences software (IBM SPSS Statistics, version 27.0) and the R Studio statistical software (v2023.12.1, R Core Team 2023) for visualization purposes. Descriptive statistics followed by normality tests and distribution asymmetry (skewness and kurtosis) revealed that the primary outcome measures

were normally distributed, while some sociodemographic characteristics were not. Hence, parametric *t* tests and nonparametric Mann-Whitney and Fisher's exact tests were used.

For study 1, consistent with our 2 × 2 study design, a repeated-measures analysis of variance (RM-ANOVA) with Greenhouse-Geisser correction was conducted, with time as within-subject and group as between-subject factors. Post hoc tests for pairwise comparisons and contrasts with Bonferroni corrections were employed. Study 2 used a 2*4 RM-ANOVA with time (T1, T2, T3, T4) as the within-subject and group as the between-subject factor. Pairwise comparisons and contrasts with Bonferroni corrections were employed.

To examine differences in opioid consumption between groups, χ^2 tests of independence were employed. Additional supporting analyses are presented in the online supplementary material. Data are presented as mean ± SD for descriptive variables (in tables) and mean ± SEM for statistical tests (in the text); statistical significance was set at α value of <0.05 for all analyses.

Results

In study 1, of 99 patients invited to participate, 80 completed the study: 38 in the RC arm; 42 in the EC arm (Fig. 1). In study 2, of 165 patients assessed for eligibility, 102 completed the study: 49 in the RC arm; 53 in the EC arm (Fig. 1). In both studies, EC and RC arms showed no significant sociodemographic differences (Table 1).

Treatment Efficacy in Study 1

Individual (Fig. 2a) and mean (Fig. 2b; online suppl. Table S1) pain scores before and after intervention for each arm are summarized. We found a significant main effect of time ($F(1, 78) = 261.907$, $p < 0.001$, $\eta^2 = 0.771$) and a significant interaction of time*group ($F(1, 78) = 22.142$ $p < 0.001$, $\eta^2 = 0.221$) but no main effect of group ($F(1, 78) = 0.82$, $p = 0.775$, $\eta^2 = 0.001$). Both arms showed a statistically significant decrease in pain intensity reports from time 1 to time 2 (RC arm: mean difference ± SE = 2.29 ± 0.289, $p < 0.001$; 95% CI = [1.714, 2.865]; EC arm: mean difference ± SE = 4.17 ± 0.275, $p < 0.001$; 95% CI = [3.619, 4.714]). Nevertheless, significant differences in pain scores emerged between arms at both time 1 (mean difference ± SE = −0.85 ± 0.344, $p = 0.016$; 95% CI = [−1.530, −0.161]) and time 2 (mean difference ± SE = 1.03 ± 0.412, $p = 0.014$; 95% CI = [0.210, 1.852]) (Fig. 2c; online suppl. Table S1).

Treatment Efficacy in Study 2

Figure 2d–f and online supplementary Table S2 depict the reduction in pain intensity and opioid consumption. Mauchly's test indicated that the assumption of sphericity was violated ($\chi^2(5) = 61.835$, $p < 0.001$). Therefore, an RM-ANOVA with Greenhouse-Geisser correction revealed a significant main effect of time ($F(2.209, 220.906) = 137.714$, $p < 0.001$, $\eta^2 = 0.579$) and significant interaction between time and arm ($F(2.209, 220.906) = 19.033$ $p < 0.001$, $\eta^2 = 0.160$) but no significant main group effect ($F(1, 100) = 1.691$, $p = 0.197$).

Pain intensity was significantly decreased from baseline across all timepoints for both arms (largest p value = 0.030), except from time 1 to time 2 ($p = 1.00$) in the RC arm. Contrasts and pairwise comparisons showed that a significant between-arms difference was found in all timepoints (largest p value = 0.045), except at time 2 ($p = 0.491$) (online suppl. Table S2). Additional supporting results for both studies are found in online supplementary material.

Opioid Consumption in Study 2

Figure 2e depicts the medication consumption in the two arms over time. A χ^2 test of independence revealed that medication consumption was significantly higher in the EC arm than that in the RC arm at time 1 ($\chi^2(1, N = 102) = 11.838$, $p < 0.001$), yet that this pattern was reversed, with significantly lower medication consumption in the EC arm than the RC arm, at time 3 ($\chi^2(1, N = 102) = 11.831$, $p < 0.001$) and time 4 ($\chi^2(1, 102) = 11.663$, $p < 0.001$). RM-ANOVAs revealed no significant main effects or interactions in any of the vital signs (see online suppl. Fig. 1S).

Discussion

These studies aimed to ecologically assess the additive analgesic value of simple verbal protocols to elicit patients' expectations of benefit from an analgesic treatment during routine clinical care. Despite differences in the studies' design and treatments, the results are surprisingly similar: when treatment included positive comments about the medication's efficacy, the analgesic effect was roughly twice that of routine medication administration. Moreover, at the last two assessments in study 2, the verbal protocol also reduced patients' opioid consumption.

The significant effect of simple verbal suggestion is not surprising. Bingel et al. [10], using the open/hidden placebo paradigm [1], clearly demonstrated that the analgesia from remifentanil is more than doubled when

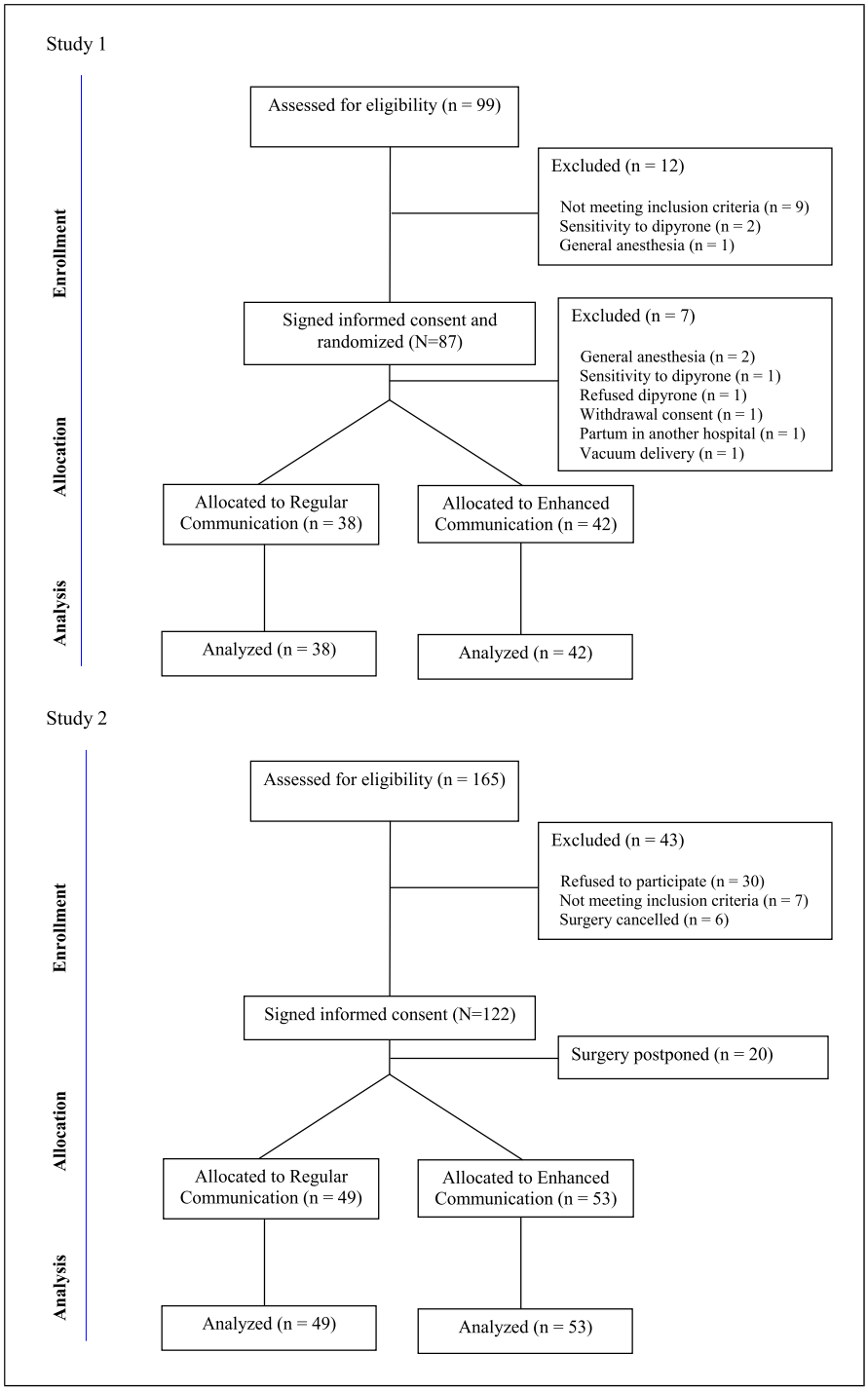

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of patients' enrolment in study 1 and study 2.

participants are aware of its administration, compared to when they are unaware. Multiple studies have demonstrated the substantial effects of verbal suggestion on pain and other symptoms [15, 20, 21, 27, 34]. The effects are not limited to pain: both subjective and objective signs representing multiple physiological systems respond to verbal suggestion [1, 6, 35]. Given this comprehensive body of evidence, this simple approach has, surprisingly, not yet been adopted in routine clinical care.

Perhaps the main barrier to harnessing the power of this verbal protocol is the lack of direct real-world, ecological evidence outside of well-controlled experimental studies.

Table 1. Sociodemographic characteristics of all participants in the two studies

Demographic and medical characteristics	All participants	RC	EC	*p* value
Study 1	*n* = 80	*n* = 38	*n* = 42	
Age, mean ± SD, years	33.86±4.54	33.37±4.82	34.30±4.28	0.364
BMI ± SD	30.48±5.07	30.28±5.14	30.66±5.07	0.741
Number of past pregnancies ± SD	2.98±1.71	2.66±1.34	3.26±1.95	0.283
Number of pregnancy failures ± SD	0.66±1.04	0.50±0.80	0.81±1.21	0.325
Study 2	*n* = 102	*n* = 49	*n* = 53	
Age, mean ± SD, years	47.68±15.96	47.05±15.45	48.26±16. 54	0.705
BMI ± SD	27.77±5.21	27.85±5.72	27.69±4.73	0.880
Gender, *N* (%)				0.914
Male	63 (38.2)	30 (61.2)	32 (62.3)	
Female	39 (61.8)	19 (38.8)	20 (37.7)	
Surgery procedure, *N* (%)				0.185
Lap. cholecystectomy	43	16 (32.7)	27 (50.9)	
Hemorrhoidectomy	6	5 (10.2)	1 (1.9)	
Hernia	42	21 (42.9)	21 (39.6)	
Submucosal resection	6	4 (8.2)	2 (3.8)	
Functional endoscopic sinus surgery	5	3 (6.1)	2 (3.8)	

Real-world results might be subject to biases and ambiguous conclusions. Our current studies might also have this limitation.

In both studies, verbal suggestion doubled the effect of analgesics routinely given for postoperative pain. This finding, however, is not conclusive. About half of the added analgesic effect observed in the EC arms of both studies was due to the greater baseline pain intensity in these arms. Possible explanations for this unexpected observation include poor or no randomization or poor or no blinding of participants and clinicians [1, 36–39].

A more conservative interpretation could dismiss the baseline differences, noting that in both studies, pain was approximately 30% lower in the EC arm than in the RC arm at the last assessment. Such a reduction in pain is clinically meaningful [40]. However, the posttreatment differences could also be due to the Pygmalion or Hawthorne effects inherent in unblinded clinical research [7]. Nonetheless, based on well-controlled experimental and clinical studies, the added analgesic effect in the two EC arms is in the expected range [19–25, 27, 28]. The current studies focused on short-term analgesia. As evident from placebo arms in chronic pain studies, placebo effects are long-lasting, suggesting that verbal suggestion should also be beneficial for chronic conditions [41].

The research community can encourage clinicians to adopt this powerful yet simple approach. Other than additional well-designed ecological studies in other painful situations, researchers could share their findings with educators to facilitate the incorporation of this topic in curricula. Healthcare students commonly learn that administering placebos is unethical, but they seldom learn that they could ethically improve outcomes during routine clinical care through verbal suggestion. Disseminating this information in all domains of healthcare will encourage the routine utilization of this simple but potentially efficacious approach [30, 31].

Some limitations deserve consideration. First, study 2's lack of randomization could contribute to the baseline pain differences. Second, data about nurses' participation and compliance were not collected. Future studies should use a dyad design to evaluate the potential effect of nurses' behavior. Third, we did not control for communication between other healthcare professionals and the participants. Fourth, nurses were not blinded for randomization and might have communicated differently (than usual) to RC participants, which could potentially result in insufficient pain relief in the RC arm. Finally, study 2's heterogenous cohort of different types of surgeries could bias the results.

To conclude, a simple verbal suggestion aimed at increasing patients' expectations of benefit from analgesic

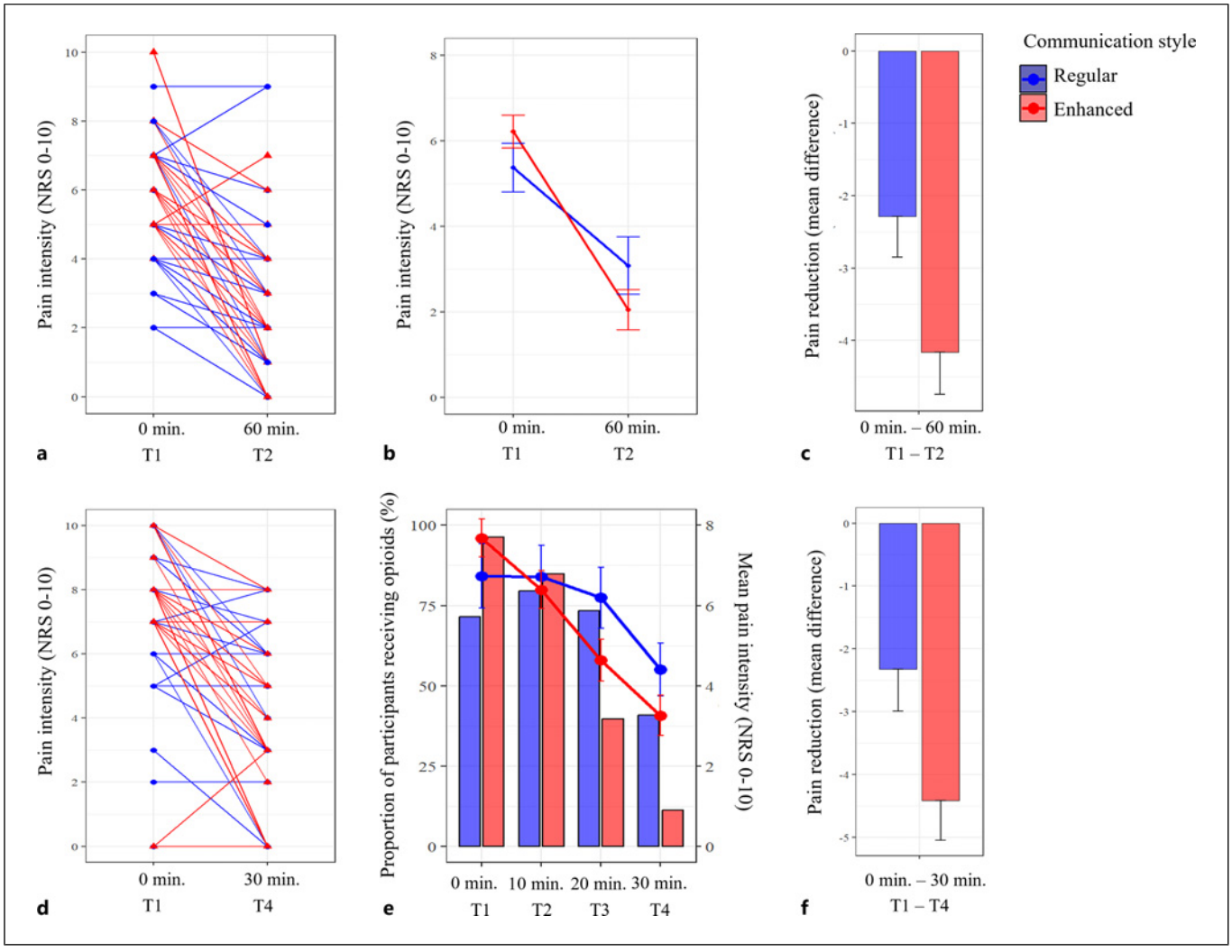

Fig. 2. Changes in pain in each study and medication consumption in study 2. Treatment efficacy results for RC arms (blue) and EC arms (red) for study 1 (**a–c**) and study 2 (charts **d–f**). **a** Individual pain intensity scores at baseline and after intervention, study 1. **b** Mean pain scores at baseline and after intervention, study 1. **c** Magnitude of pain reduction (mean difference), study 1. **d** Individual pain intensity scores at time 1 (0 min) and time 4 (30 min, last timepoint of assessment), study 2. **e** Proportion of participants consuming analgesics (left side *y*-axis, bar plot represents percentage of opioid consumption across time) and mean pain intensity across time (right *y*-axis, line plot represents pain intensity), study 2. **f** Magnitude of pain reduction (mean difference between first and last assessments), study 2. Error bars signify confidence interval at 95%.

treatment doubles its analgesic effect or, more conservatively, increases it by approximately 30%. This enhanced response could reduce suffering and improve treatment outcomes at no cost, for both the treatment of pain and beyond.

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Statement of Ethics

Both studies received approval from each hospital's Helsinki Committee (study 1: 0014-23-CMC; study 2: 0128-22-ZIV) and Ethics Committee (University of Haifa, study 1: No. 172/23; study

2: No. 213/23) and were preregistered on Clinicaltrials.gov (study 1: NCT05970029; study 2: NCT06258239). All participants signed informed consents before entering the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.T. planned the studies; oversaw all the studies' activities, data processing, and data analysis; and wrote the first draft. V.C. and L.I. managed data collection and contributed to the manuscript preparation. M.A. assisted with data processing, data analysis, and the preparation of the Results section of the manuscript. K.B.W. and A.I. assisted with regulatory perspectives and reviewed the manuscript. All the co-authors reviewed the manuscript and approved its final version.

Data Availability Statement

The two anonymized data files of the two studies can be downloaded via this link: https://osf.io/78ypq/?view_only=b4d65ac44fc3429bb7625f4ffb530e69.

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