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Nocebo effects on motor performance: A systematic literature review

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Directionally opposite to placebo effects are the nocebo effects that negatively impact people's thoughts, feelings, and actions. An important but scarcely studied aspect of everyday functioning is motor performance, in which nocebo effects might impair athletic skills and the much-needed purposeful daily movements and motor actions. The aim of this literature review is to unveil the nocebo effects on motor performance.

Searched databases were PubMed, PsycINFO, and SPORTDiscus. Twenty-one articles, reporting 23 studies, met the eligibility criteria for inclusion in the current review. All reports exhibited "some" risk of bias. Of the 23 studies, 14 found a nocebo effect on motor performance, equivocal results emerged from two studies, and negative findings were reported in seven studies. Most (10/12) studies using a between-subjects design have reported a nocebo effect. The mean effect size was 0.60, suggesting a medium-to-large effect of nocebo intervention on motor performance. Based on this review, we conclude that nocebo effects do influence motor performance and can be evoked with negative verbal information. This effect may be more robust than the placebo effect but also depends on the type of motor performance, on the examined sample, and on the nocebo agent. Hence, nocebo effects should be recognized and controlled in empirical research on motor performance, and they should be prevented or extinguished in practical and therapeutic settings. More extensive examination of the nocebo effect on motor performance is warranted, especially using between-subjects research design and a "no agent" control condition.

Key words: Expectation, motor performance, placebo effect, psychomotor performance, sport performance.

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INTRODUCTION

The term placebo originates from the Latin language; *placere* means "to please." The term nocebo has the same origin, *nocere* means "to harm" (Kennedy, 1961; Kissel & Barrucand, 1964). The placebo response can be defined as a positive outcome resulting from the persons' expectations, schematic reactions, and conditioned responses that can interact with each other and work both on a conscious or non-conscious level (Bartels, van Laarhoven, Heijmans et al., 2017; Beedie, Benedetti, Barbiani et al., 2018; Colloca, Sigaudo & Benedetti, 2008; Stewart-Williams & Podd, 2004). In a similar vein, negative expectations, schematic reactions, and conditioned responses can trigger negative (i.e., not desirable and unpleasant) effects, that is, a nocebo response (Colloca & Barsky, 2020; Petrie & Rief, 2019). Originally, nocebo effects referred to the side effects evoked by placebos; later, these were conceptualized as negative changes triggered by expectations of harmful changes and the accompanying emotions (Hahn, 1985, 1997). This latter approach assumes the existence of conscious and non-conscious expectations that manifest themselves as unpleasant or even harmful mental and physical states.

Placebo and nocebo responses have been shown to play an important role in many health and performance-related areas of life. These can be induced by evoking positive or negative expectations, most often by providing positive or negative information about the effect of an inert or a real treatment (Benedetti, 2009). In the medical context, the placebo response primarily refers to the reduction of subjective somatic symptoms, anxiety, depression, and pain (Benedetti, 2011; Hróbjartsson & Gøtzsche, 2001, 2010; Kaptchuk & Miller, 2015; Petersen, Finnerup, Colloca et al., 2014), but it can result in objective clinical improvement too (e.g., Kemeny, Rosenwasser, Panettieri, Rose, Berg-Smith & Kline al., 2007; Wilhelm, Winkler, Rief & Doering, 2016). The nocebo response has the opposite effects, which can lead to considerable suffering, non-adherence and increased drop-out in clinical settings and trials (Barsky, Saintfort, Rogers & Borus, 2002; Colloca & Barsky, 2020; Petrie & Rief, 2019), and may also result in fall incidents (Winblad, Kilander, Eriksson et al., 2006), breathing restrictions (Schenk, 2008) and impaired mobilization (Zech, Seemann, Grzesiek, Breu, Seyfried & Hansen, 2019). Beyond medical settings, the placebo and nocebo phenomena can impact the physiological, behavioral affective, and cognitive functioning of healthy individuals, too (Colloca & Barsky, 2020; Drici, Raybaud, Lunardo, de, Iacono & Gustovic, 1995; MacKrill, Gamble, Bean, Cundy & Petrie, 2019; Mlynski, Wright & Kelly, 2020; Petrie & Rief, 2019; Schmid, Theysohn, Ga *et al.,* 2013; Turi, Bjørkedal, Gunkel, Antal, Paulus & Mittner, 2018). The current systematic review focuses on the nocebo effect with respect to another important yet much-overlooked area: motor performance. There is one aspect of motor performance, namely sports performance, for which a systematic review on placebo and nocebo effect has been conducted (Hurst, Schipof-Godart, Szabo *et al.,* 2019). However, motor performance is a broader term, incorporating not only the execution of sport-specific movements but also including skills that are essential to normal everyday functioning, such as simple reaction time or vigilance. To our knowledge, this review is the first to date that focuses on motor performance-related nocebo responses. In this

review, we define motor performance as the ability to complete a well-defined and observable motor task that involves the activity of the skeletal muscles. Performance is defined as "goal-centered, purposeful, observable behavior of a relatively short duration" (Martens, 1971, p. 152).

Motor performance plays an essential role in many areas of life. There are clinical conditions in which a drop in motor functioning is an indicator of worsening (Poewe *et al.,* 2017). For example, it was shown that the nocebo effect could worsen motor functions in Parkinson's disease (Mestre, Lang & Okun, 2016; Rato, Duarte, Ferreira *et al.,* 2019). Such deterioration may be critical when the patient becomes unable to maintain everyday activities, which has a clear negative impact on their quality of life. Also, psychotic conditions can be accompanied by impaired motor performance (Mittal, Bernard & Northoff, 2017; Walther & Mittal, 2017; Walther & Strik, 2012). Psychomotor performance (i.e., a highly complex motor behavior resulting from the cognitive processing of sensory and perceptual information; Hindmarch, 2010) influences important aspects of everyday life for healthy individuals too. For example, in situations like driving a car or riding a bicycle, it is crucial to react quickly and appropriately. Beyond professional athletes, for whom a high level of physical achievement is of uttermost importance for their carrier and living, proper motor functions are required in almost all areas of everyday life. Nocebo effects can negatively impact relatively simple movements, which can lead to impaired functioning, and negative psychological consequences, such as lower self-esteem and self-efficacy (Sonstroem & Morgan, 1989; Sonstroem, 1997).

The nocebo response is basically a top-down type reaction, in which knowledge and beliefs impact perception and even physiological functioning (Cannon, 1957; Hahn, 1985, 1997). As motor performance is also partly determined by central functions, it can also be malleable to nocebo influences (Carlino, Piedimonte & Frisaldi, 2014). From a neuropharmacological perspective, these may influence the functioning of different neurotransmitter systems, such as the opioid, endocannabinoid, serotonin and dopamine systems (Beedie, Benedetti, Barbiani, Camerone, Lindheimer & Roelands, 2019; Benedetti, 2011; Colloca & Barsky, 2020). Changes in these systems can have a direct effect on physical performance, for example, by modulating pain, anxiety, and motivation, respectively (Beedie *et al.,* 2019). Moreover, it was found that nocebo interventions can modulate the functioning of different brain regions involved in movement control, such as the primary motor cortex and supplementary motor area (Fiorio, 2018). Also, the central governor model states that psychological and other top-down factors can modify fatigue, as it is not a reaction to the failure of homeostasis but an emotion that motivates the organism to cease exercise before any damage develops (Carlino *et al.,* 2014; Noakes, 2007). Accordingly, nocebo can alter the evaluation of muscle performance and decrease fatigue threshold, thus impairing motor performance (Carlino *et al.,* 2014). From a practical standpoint, athletes use different techniques that act through top-down mechanisms to boost their performance, such as "psyching up" (Shelton & Mahoney, 1978; Tod, Iredale, McGuigan, Strange & Gill, 2005) and hypnosis (Liggett, 2000; Newmark & Bogacki, 2005). Consequently, many empirical studies reported the existence of placebo and nocebo effects in different aspects of motor performance (Beedie, Coleman & Foad, 2007; Benedetti, Pollo, Lopiano, Lanotte, Vighetti & Rainero, 2003; Bérdi, Köteles, Szabó & Bárdos, 2011; Corsi, Emadi Andani, Sometti, Tinazzi & Fiorio, 2019; Hurst *et al.,* 2019; Winkler & Hermann, 2019). However, the findings are inconsistent because there are studies that report no effect (Keitel, Ferrea, Sudmeyer, Schnitzler & Wojtecki, 2013) or inconclusive findings (Harrell & Juliano, 2009).

Despite the heavy and sometimes detrimental impact of the nocebo phenomenon on everyday functioning (Colloca & Barsky, 2020; Mitsikostas, Mantonakis & Chalarakis, 2011; Petrie & Rief, 2019), the placebo effect receives more research attention. For example, in a recent systematic review, only five articles were found that investigated the nocebo effect in sports performance, while 27 articles investigated the placebo effect (Hurst *et al.,* 2019). It is important to note that mechanisms and results explored while studying placebo responses cannot be generalized to the nocebo phenomenon. The two mechanisms are not necessarily the simple opposites of each other (Freeman, Yu, Egorova *et al.,* 2015). For example, it was shown that a placebo procedure in force production enhanced the amplitude of the motor evoked potentials and reduced the cortical silent period's duration (Fiorio, Andani, Marotta, Classen & Tinazzi, 2014). However, the nocebo procedure did not cause a change in the amplitude of the motor evoked potentials, and also reduced the cortical silent period (Emadi Andani, Tinazzi, Corsi & Fiorio, 2015). Furthermore, a neuroimaging study has shown that a nocebo intervention impacts the brain differently from a placebo intervention, including the activation of the hippocampus and regions involved in anticipatory anxiety (Kong, Gollub, Polich *et al.,* 2008). From a theoretical perspective, aspects of healthy functioning cannot be improved beyond a certain limit, whereas there is much more room to worsen them. Thus, it is also legitimate to argue that the nocebo effect may even be larger in the negative direction than placebo effects in the positive direction (Greville-Harris & Dieppe, 2015; van Laarhoven, Vogelaar, Wilder-Smith *et al.,* 2011). This argument might hold particularly true for motor performance, which needs a fine and precise timed cooperation of many brain regions and are sensitive to anxiety (Martens, Vealey & Burton, 1990; Mullen, Hardy & Tattersall, 2005; Nieuwenhuys & Oudejans, 2017). Furthermore, in contrast to vegetative and affective functions, motor performance can be directly and voluntarily controlled, thus loss of motivation can also heavily impact it (Beedie *et al.,* 2019). Because of the aforementioned reasons, it is important to develop an independent understanding about the nocebo effect just as deep as we have about the placebo effect (Colloca & Barsky, 2020).

METHODS

Search strategy

The review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati, Altman, Tetzlaff *et al.,* 2009). Table 1 summarizes the search and selection strategy. As keywords, we used "nocebo" or "negative placebo" combined with "motor" or "muscular" or "sport*" or "exercise" or "performance" or "movement" or "skill." The search engine was set to scan the whole articles (title, abstract, and text) for the keywords. Searching was conducted in three different databases: PubMed, PsycINFO,

and SPORTDiscus. Additionally, 27 studies were added from other sources (e.g., previous literature reviews). We performed the screening in July of 2020. No time filter was used, but only English articles were included. In an effort to keep the quality of the articles high, only papers in peer-reviewed journals were eligible. Thus, for example, dissertations and conference materials were excluded. The determination of the inclusion criteria was based on the PICO (population, intervention, control, outcome) standard. We did not use any restrictions with respect to the participants. A study was eligible only if an explicit nocebo intervention or suggestion was used, where the goal was to elicit a reduction in performance based on top-down mechanisms, for example by verbal suggestion about the performance decreasing effect of an inert substance (intervention), which was then compared to a control group (control). The outcome variable had to assess motor performance which we defined as the ability to perform a measurable motor task (i.e., one that involves the work of the skeletal muscles). Performance was defined as "goal centered, purposeful, observable behavior of a relatively short duration" (Martens, 1971, p. 152).

Effect size

To determine the magnitude of the nocebo effect, we used effect size calculation. We decided not to compare the effect size of studies with very different designs. For example, in certain studies, the control group did not receive the same inert substance that was used as a nocebo agent in the experimental group. In other studies, the control group received the same agent as the experimental group (e.g., inert substance) but without any information about its effect. Receiving an agent without information or not receiving it at all may have different consequences, which may lead to substantially different effect sizes. For this reason, effect sizes were calculated only for studies that compared nocebo to a no agent condition, which shows the natural course of the studied phenomenon. Effect sizes were calculated with Morris (2008) d_{ccp2}sensu formula, which takes into account the pre-treatment difference between the experimental and control group. Where the pre-treatment means and standard deviations of the groups were not available, Cohen's *d* was calculated.

Risk of bias

With the RoB 2.0 tool (Higgins, Altman, Gøtzsche *et al.,* 2011; Sterne, Savović, Page *et al.,* 2019), we assessed the risk of bias of the included studies in five different domains: (1) insufficiencies in the randomization process; (2) deviations from intended intervention; (3) missing outcome data; (4) measurement of the outcome data; and (5) selective reporting of the results. To evaluate the studies, one has to answer different questions with "Yes," "Probably yes," "Probably no," "No" or "No information" statements. The outcome of the algorithm is "low concern," "some concern," or "high risk of bias." The authors repeatedly evaluated the studies for consistency.

Table 1. *Summary table of the search and selection strategy*

Used keywords	- "Nocebo" OR "negative placebo" AND - "Motor" OR "muscular" OR "sport*" OR "exercise" OR "performance" OR "movement" OR "skill"
Searched datasets	PubMed, PsycINFO, SPORTDiscus
Time filter	None
Language filter	English only
Document type filter	Articles in peer-reviewed journals
Inclusion criteria	**P**opulation: any human population **I**ntervention: the intervention must contain explicit nocebo intervention or suggestion **C**omparison: nocebo intervention has to be compared with placebo or control condition or group **O**utput: outcome variable has to assess motor performance
Exclusion criteria	Reviews, Dissertations, Not empirical papers, Conference materials, Not English papers, Not peer reviewed papers

RESULTS

Included articles

In total, 322 studies were found in the databases, and 27 were added from other sources. After removing the duplicates, 295 studies were screened. Based on their title and abstract, 266 studies were excluded because they did not fulfill the inclusion criteria: these were not English-language articles, were not published in a peer-reviewed journal, or did not contain nocebo intervention objective measurement of motor performance. The full text of the remaining 29 articles was read, and further four studies were excluded because the intervention lacked explicit nocebo intervention or suggestion, and four studies because the outcome variable did not assess objective motor performance. Overall, 21 articles were found to be eligible for the systematic review. There were two papers (Piedimonte, Guerra, Vighetti & Carlino, 2017; Pollo, Carlino, Vase & Benedetti, 2012) that reported the results of two independent studies. Thus the overall number of studies included in this review was 23 (Table 2). Figure 1 illustrates the selection process.

Risk of bias

The risk of bias judgment, resulting from the randomization process was "Some concerns" for all but two studies, generally because the allocation sequence was not fully random or it was not concealed. For every study, deviations from intended intervention, missing outcome data, and measurement of the outcome showed "Low concern." The risk of bias resulting from the selection of reported results was "Some concerns" for every study, mainly because of the procedure and the statistical analysis was not preregistered. In consequence, the overall risk of bias was "Some concerns" for every included study. See Table 3 for details.

Characteristics of the included studies

Overview. Here we refer to the studies based on their number in Table 1. In this systematic review, out of the 23 included studies, 14 reported that nocebo intervention negatively impacted motor performance (2, 3, 4, 6, 7, 8, 12, 14, 16, 19, 20, 21, 22,23). Equivocal results were found in two (1, 5), and no nocebo effect was revealed in seven (9, 10, 11, 13, 15, 17, 18). To further explore the results, the studies were categorized with respect to: (1) the nocebo agent they used; (2) the outcome variable and population they assessed; (3) the condition to which nocebo condition was compared; and (4) study design.

Nocebo agent. The most widely used nocebo agents were non-effective sham transcutaneous stimulation and inert substances. Of the seven studies in which non-effective or sham transcutaneous electrical stimulation was used, five reported a nocebo effect (7, 8,

Table 2. *Review table of the included studies in ascending chronological order*

Article number, author, year	Sample (*N*, *M* age ± *SD*, % female)	Design	Nocebo agent	Conditions	Outcome measure	Results (effect size [d] if available)
1. Snyder, Schulz, and Jones (1974)	University students (36, ?, 25%)	BS	Perceived duration of exercise with or without temporal standard	Longer (nocebo) or shorter (placebo) instruction	RT	No standard: established with standard: opposite effect
2. Fillmore, and Vogel-Sprott (1992)	University students (56, range: 19–29, 0%)	BS	Sham caffeine	Nocebo, placebo, no effect instruction or no agent	Pursuit rotor task performance	Established [0.69]
3. Benedetti *et al*. (2003)	Parkinson's patients (10, 60.8 ± 8.1, 40%)	CO	Sham-changing deep-brain stimulation intensity with preconditioning	Nocebo, placebo instruction or no information	RT	Established
4. Beedie *et al*. (2007)	Athletes (42, 19.6 ± 2.9, ?)	BS	Sham-ergogenic aid	Nocebo or placebo instruction	30 m sprint time	Established
5. Harrell and Juliano (2009)	Adult coffee consumers (60, 22.6 ± ?, 68%)	BS	Sham-coffee or real coffee	Placebo or nocebo instruction	Vigilance RT; finger tapping	Coffee: opposite effect sham coffee: established
6. Colagiuri, Livesey, and Harris (2011)	University students (464, range: 17–56, 66%)	CO	odor	Placebo, nocebo instruction or no information	Implicit learning task RT	Established
7. Pollo *et al*. (2012), study 1	Healthy individuals (30, 22.53 ± 2.14, 0%)	BS	Sham sub-threshold electrical stimulation	Nocebo or no agent	Leg extension exercise	Established [0.57*]
8. Pollo *et al*. (2012) study 2	Healthy individuals (37, 20.46 ± 1.03)	BS	Sham sub-threshold electrical stimulation with preconditioning	Nocebo or no agent	Leg extension exercise	Established [0.69*]
9. Keitel *et al*. (2013a)	Parkinson's patients – hypokinetic-rigid (24, 62.83 ± 9.3, 50%)	CO	Sham changing in deep-brain stimulation intensity (with or without medication)	Placebo, nocebo instruction and no information	Diadochokinesia; finger tapping	No established
10. Keitel *et al*. (2013b)	Parkinson's patients – tremor dominant (24, 64.2 ± 7.8, 21%)	CO	Sham-changing deep-brain stimulation intensity (with or without medication)	Placebo, nocebo and no information	Diadochokinesia; finger tapping	No established
11. Bottoms, Buscombe, and Nicholetto (2014)	Healthy individuals (12, 25.3 ± 4.4, 0%)	CO	Non-sugar drink	Placebo, nocebo instruction and no information	Peak power in arm ergometry	No established
12. Emadi Andani *et al*. (2015)	Healthy individuals (32, 21.1 ± 2.2, 50%)	BS	Transcutaneous electrical nerve stimulation with preconditioning	Nocebo or no effect instruction	Maximal force	Established
13. Schwarz and Büchel (2015)	Healthy individuals (37, 25.2 ± 5.7, 59%)	CO	Tone frequencies with preconditioning	Nocebo, placebo and no effect instruction	Flanker task RT	No established
14.Corsi *et al*. (2016)	Healthy individuals (41, 22.6 ± 3.1, 44%)	BS	Transcutaneous electrical stimulation with preconditioning	Nocebo or no effect instruction	Maximal force	Established
15. Fresson, Dardenne, Geurten, Anzaldi, and Meulemans (2017)	University students (80, 22.7 ± 3.1, 52.5%)	CO	Light	Placebo, nocebo and no effect instruction	Attention score	No established
16. Hurst *et al*. (2017)	Athletes (712, range: 18–44, 22%)	BS	Inert capsule	Nocebo, placebo or no agent	20 m sprint time	Established [0.32]
17. Piedimonte *et al*. (2017), study 1	Right handed university students (17, ?, ?)	CO	Sham pain-reducing electrodes	Nocebo and placebo instruction	Pain-avoidance RT	No established
18. Piedimonte *et al*. (2017), study 2	Right-handed university students (17, ?, ?)	CO	Sham pain-reducing electrodes with preconditioning	Nocebo and placebo instruction	Pain-avoidance RT	No established
19. Turi *et al*. (2018)	Healthy individuals (80, 24.61 ± 3.53, 0%)	BS	Sham non-invasive brain stimulation with preconditioning	Nocebo or placebo instruction	Probabilistic learning task RT	Established
20. Corsi *et al*. (2019)		BS			Maximal force	Established

(continued)

Table 2. (continued)

Article number, author, year	Sample (*N*, *M* age ± *SD*, % female)	Design	Nocebo agent	Conditions	Outcome measure	Results (effect size [d] if available)
	Healthy university students (53, 22.32 ± 2.5, 53%)		Transcutaneous electrical nerve stimulation with positive or negative preconditioning	Nocebo or placebo instruction		
21. Winkler and Hermann (2019)	Healthy individuals (75, 22.7 ± 3.8, 65.3%)	BS	Non-effective nasal spray	Placebo or nocebo or no agent	Alertness RT with or without warning signal	established [warning: 0.17*, without warning: 0.16]
22. Zech *et al*. (2019)	Healthy individuals (?, range:18–70, ?)	CO	Words, sentences situations	Placebo, nocebo and neutral	Maximal force	Words: no established Sentences: established Situations: established
23. McLemore *et al*. (2020)	Healthy individuals (14, 20.5 ± 0.9, 0%)	BS	Inert capsule	Nocebo or no agent	Biceps curl total repetitions	Established [1.57*]

Notes: Design: BS = between subjects; CO = crossover.
Outcome measure: RT = reaction time.
Result: established: nocebo effect established, no established: nocebo effect not established, opposite direction: nocebo agent improved performance.
Effect sizes are presented only if nocebo was compared to no agent condition *effect size established with Morris (2008) dccp2sensu formula, to control for pre-treatment differences. In every other case, Cohen's d was calculated.
?no information.

12, 14, 20), whereas two did not (17, 18). Also, seven studies applied inert substances to evokea nocebo response. In one of these, real caffeine was also used alongside sham caffeine (5). In five studies, a significant nocebo effect was found (2, 4, 16, 21, 23), no effect was found in one (11), and results were equivocal in another study (5). Four studies applied sham deep brain stimulation or a sham change in its intensity. A nocebo effect was revealed in two studies (3, 19), whereas no impact was found in the other two (9, 10). In three studies, other physical stimuli (odor, tone, light) were used to elicit a nocebo effect, and only one was able to do so (6); the other two were not (13,15). Only one study used solely verbal information about exercise duration and reported ambiguous results (1). Another study used verbal and visual information, and a nocebo effect was found (22).

Outcome variable and study population. In 10 studies, the psychomotor performance of healthy individuals was investigated, for example, complex or simple reaction time. Four of these revealed the effectiveness of the nocebo intervention (2, 6, 19, 21), four reported null-findings (13, 15, 17, 18), and two reported ambiguous results (1, 5). Furthermore, 10 studies investigated the sport performance of healthy individuals. Nine of these revealed a nocebo effect (4, 7, 8, 12, 14, 16, 20, 22, 23), and one did not (11). The remaining three studies were conducted in Parkinson's patients. The outcome variables measured reaction time, finger tapping or diachokinesia (i.e., altering pronation-supination movements of the hand as fast, smoothly, and far as possible while holding a wooden bar). Only one study reported a nocebo effect (3); the other two did not (9, 10).

Control condition/group. In six studies, the control was a no-intervention condition, where no agent, information, or conditioning was delivered. All of these reported a nocebo effect (2, 7, 8, 16, 21, 23), with a mean effect size of 0.60. In four studies, the "no effect instruction" group served as control, where an inert agent was delivered with the information that it would not affect participants' performance. Of these, two found a nocebo effect (12, 14), the other two did not (13, 15). Five studies used a "no information" control, where an agent was delivered without any information about its effect on performance. From those, two evoked a nocebo reaction (3, 6), but three did not (9, 10, 11). Seven studies applied the placebo condition as a comparison, where basically the same agent was delivered as for the nocebo group, but opposite (positive) expectations were elicited. Three of these found a nocebo effect (4, 19, 20), two reported ambiguous results (1, 5), and two could not establish the nocebo effect (17, 18). One study applied a neutral condition (neutral words, sentences, and situations) as control, and the nocebo effect was established (22).

Design. In 13 studies, the between-subjects design was used to investigate nocebo effect in motor performance. From these, 11 reported a nocebo effect (2, 4, 7, 8, 12, 14, 16, 19, 20, 21, 23), and two found ambiguous results (1, 5). Ten studies applied a within-subjects (crossover) design of which, only three could reveal a nocebo effect (3, 6, 22), and seven did not (9, 10, 11, 13, 15, 17, 18).

DISCUSSION

In this systematic review, 21 scholastic papers reporting the findings of 23 empirical studies on the nocebo effect, with respect to motor performance, were reviewed. It is important to note that we included a study only if an explicit nocebo intervention was used and if it was compared to a placebo or a control group. For this reason, empirical studies using different paradigms (e.g., open-hidden paradigm) were not included, which may be a limitation of this review. The included studies were different in many aspects, such as the outcome variable, the sample, and

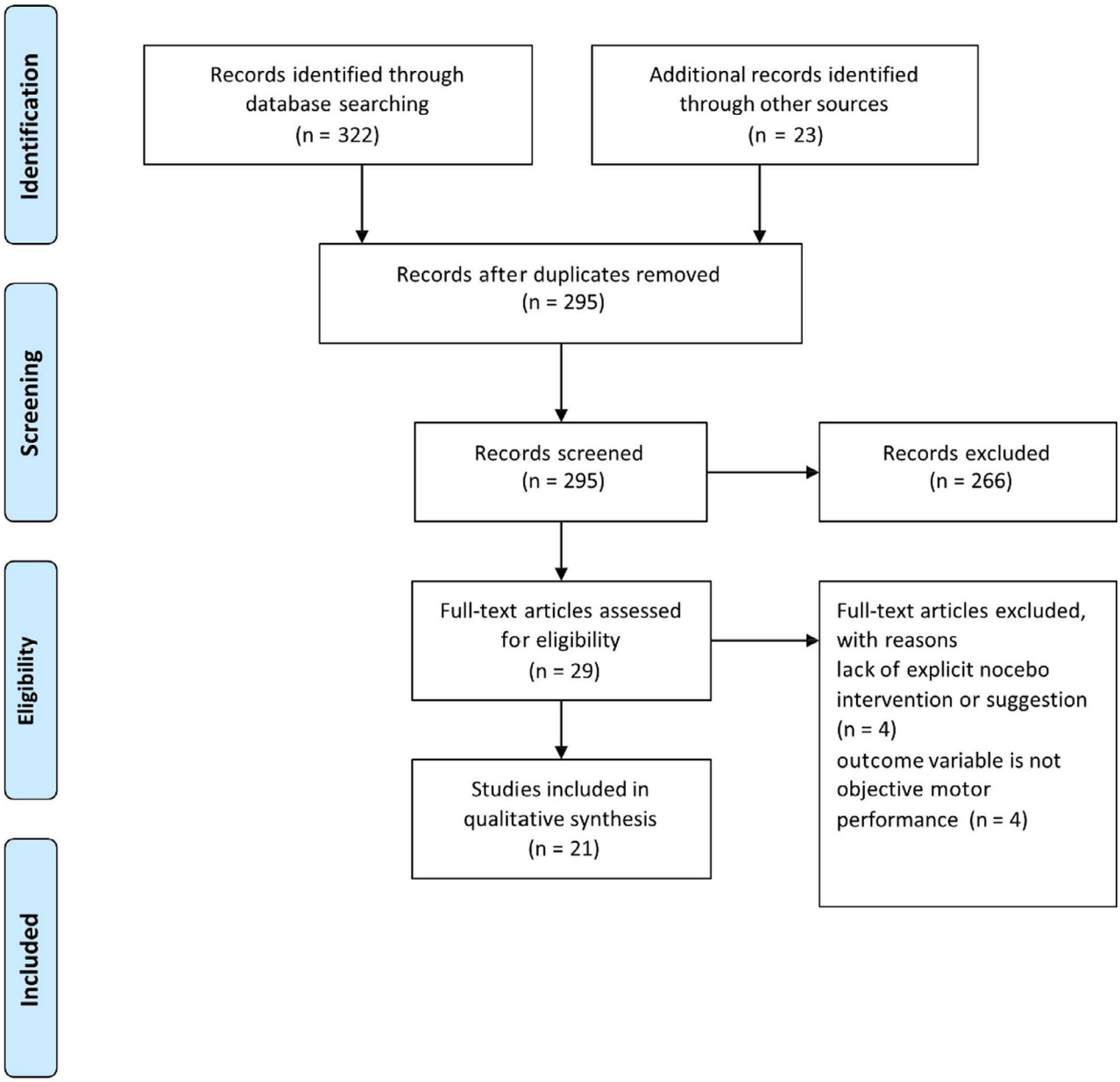

Fig. 1. Selection of studies, based on Moher, Liberati, Tetzlaff, Altman, and the PRISMA Group (2009).

methodological details, such as study design, the control condition to which nocebo condition was compared, and the risk of bias. We will start the discussion with the methodological aspects.

Nocebo condition was either compared to a condition receiving no agent (no agent condition), receiving the same agent with the information that it would not affect the performance (no effect instruction), receiving the agent without any information (no information condition), or receiving the agent, but with placebo instruction (placebo instruction). For investigating the nocebo effect in motor performance, we argue that the "no agent condition" is the most desirable as a control condition because of its high ecological validity. In more detail, the practical question behind nocebo studies is whether an agent that evokes negative expectations is able to impair performance in comparison to the condition when nothing special happens. Disentangling the agent and the information is not a desirable methodological step when one is curious about the overall effect of this "package." Delivering an agent to the control group may appear to be good to make the conditions more comparable from a methodological point of view or even necessary if one wants to investigate the effect of the instruction, for example, using the so-called balanced placebo design. However, even with the explicit information that it will not affect performance, such agents may elicit a nocebo/placebo reaction through non-conscious, automatic responses (Bartels *et al.,* 2017; Stewart-Williams & Podd, 2004). Delivering the agent without any information (no information condition) gives place to even more ambiguity, as the effect will be determined by the expectations and spontaneous associations of the participants. Methodologically the most inappropriate design is the simple comparison of the nocebo and the placebo

Table 3. *Evaluation of the risk of bias in different domains and overall, indicating low concern, some concern, high concern. Based on Higgins et al. (2011)*

Author, year	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported result	Overall
1. Snyder *et al.* (1974)	Some	Low	Low	Low	Some	Some
2. Fillmore and Vogel-Sprott (1992)	Some	Low	Low	Low	Some	Some
3. Benedetti *et al.* (2003)	Some	Low	Low	Low	Some	Some
4. Beedie *et al.* (2007)	Some	Low	Low	Low	Some	Some
5. Harrell and Juliano (2009)	Low	Low	Low	Low	Some	Some
6. Colagiuri *et al.* (2011)	Some	Low	Low	Low	Some	Some
7. Pollo *et al.* (2012)	Some	Low	Low	Low	Some	Some
8. Keitel *et al.* (2013a)	Some	Low	Low	Low	Some	Some
9. Keitel *et al.* (2013b)	Some	Low	Low	Low	Some	Some
10. Bottoms *et al.* (2014)	Some	Low	Low	Low	Some	Some
11. Emadi Andani *et al.* (2015)	Some	Low	Low	Low	Some	Some
12. Schwarz and Büchel (2015)	Some	Low	Low	Low	Some	Some
13. Corsi *et al.* (2016)	Some	Low	Low	Low	Some	Some
14. Fresson *et al.* (2017)	Some	Low	Low	Low	Some	Some
15. Hurst *et al.* (2017)	Low	Low	Low	Low	Some	Some
16. Piedimonte *et al.* (2017)	Some	Low	Low	Low	Some	Some
17. Turi *et al.* (2018)	Some	Low	Low	Low	Some	Some
18. Corsi *et al.* (2019)	Some	Low	Low	Low	Some	Some
19. Winkler and Hermann (2019)	Some	Low	Low	Low	Some	Some
20. Zech *et al.* (2019)	Some	Low	Low	Low	Some	Some
21. McLemore *et al.* (2020)	Some	Low	Low	Low	Some	Some

condition. Even if there is a significant difference between the groups, one cannot figure out if it is due to the placebo effect, the nocebo effect, or both. A no agent condition is also desirable because it shows the natural course of the studied domain. Thus, it helps exclude any confounding factors resulting from any manipulation (e.g., from any substance, conditioning, or verbal information) or additional non-controlled factors.

From a methodological perspective, the study design is also important. In this review, studies using a crossover design dominantly resulted in null findings (seven of 10 studies). In contrast, most of the studies (10 out of 12) using parallel group between-subjects design established a nocebo effect. The reason for the increased number of null findings in crossover studies may be that participants repeatedly performed the same motor task. The positive effect of practice on performance, together with the possible positive expectation evoked by the practice, may interfere with nocebo response. As we are not aware of any empirical study that would specifically test this hypothesis, this idea is admittedly speculative.

The quality of the included studies was similar with respect to the Risk of Bias (Higgins *et al.,* 2011; Sterne *et al.,* 2019). Deviations from intended intervention, missing outcome data, and the measurement of the outcome data resulted in a low risk of bias for every study. However, to minimize the risk of bias, researchers should pay more attention to the use of a fully random sequence for randomization and make the sequence concealed to both participants and investigators. Also, it would be desirable to predetermine the process of the data analysis with preregistration.

Beyond methodological considerations, results may depend on the outcome variable and the investigated population too. Motor performance is a broad term, incorporating tasks from maximal force production to the speed of response. In this systematic review, concerning the outcome variable and population, studies could be categorized into three groups. Most of the studies (11) investigated the psychomotor performance of healthy individuals, and a relatively small proportion of these (four of them) reported a nocebo effect. The second group of studies investigated healthy individuals' sport performance (mainly force production and speed), where in most cases, a nocebo effect was established. The third group of studies investigated the psychomotor performance of patients with Parkinson's disease, where only reaction time, but not finger tapping and diadochokinesia was found to be modulated by the nocebo effect. Based on these findings, we can conclude that healthy individuals' sports performance seems to be the most susceptible aspect of motor performance to nocebo influences.

The nocebo effect may depend on the agent that is used to evoke it too. The study of Zech *et al.* (2019), where negative words did not, whereas negative sentences and situations did elicit a nocebo response, illustrates this point very well. It is also essential to consider if an active or a non-active agent is used, as shown by the study of Harrell and Juliano (2009). Interestingly, real caffeine with nocebo instruction increased performance, but sham caffeine with the very same instruction decreased it (Harrell & Juliano, 2009). This finding shows that specific (pharmacological) and non-specific effects can interact with each

other in some instances (Dömötör, Szemerszky & Köteles, 2014). To establish a "pure" nocebo effect, in most studies, non-active, sham treatments were used. In this review, studies using sham transcutaneous electrical stimulation and inert substances were the most likely to elicit a nocebo effect.

Overall, it can be concluded that it is possible to evoke a nocebo effect in motor performance. These expectations are usually elicited by delivering a sham agent with verbal instruction that it will worsen performance. In some cases, a conditioning procedure is also used. Corsi *et al*. (2019) found that verbal information about performance worsening can overwrite positive conditioning, so verbal instruction had a stronger effect on motor performance than conditioning. They also concluded that the nocebo effect is more robust than the placebo effect (Corsi *et al.,* 2019), which is also demonstrated by Hurst *et al*. (2017). Nocebos can act through neurobiological mechanisms: by inhibiting opioidergic and dopaminergic neurological systems (resulting in an increased level of pain and a decreased level of motivation, respectively), and activating the cholecystokinin system (resulting in an increased level of anxiety), which has a clear negative effect on motor performance (Beedie *et al.,* 2019). Another possible mechanism is the increase of fatigue through central mechanisms (Carlino *et al.,* 2014).

Although the nocebo effect seems more robust than the placebo effect in motor performance (Corsi *et al.,* 2019; Hurst *et al.,* 2017), it is comparatively rarely studied (Hurst *et al.,* 2019). Hence further research in this field is warranted. For researchers, it is to use proper research techniques to reveal and explain nocebo effects that are generalizable to everyday situations. The importance of the appropriate control group in nocebo and placebo research is also highlighted by Colloca and Barsky (2020), the inclusion of a no-intervention group appears to be the best option. Beedie *et al*. (2018) also proposed that using no-treatment groups alongside placebo and/or nocebo groups in motor research would help understand these effects. We also recommend that researchers use a no agent condition as a control condition because of its validity and the problems with other kinds of control groups (i.e., uncontrolled, confounding effects if some sort of agent and/or information is delivered). It is important to highlight that each study, included in this review, used a no agent control group to establish the nocebo effect. Also, as Benedetti (2009) suggested, it may also be desirable to use more complex designs (i.e., comparing multiple groups, receiving different treatments) to explore placebo and nocebo effects in their complexity. In doing so, different experimental and control procedures become comparable. Moreover, we recommend using parallel groups (between-subjects) design because there is a possibility that repeated testing on the same motor task in a crossover design interferes with the nocebo effect. The quality of research in this field could be improved by minimizing the risk of bias by predetermined data analysis and using full-random, concealed sequences with the randomization procedure. These assumptions can be generalized to investigations of the placebo effect in motor performance too.

These findings are important from a practical point of view, as motor performance plays an inherent role in many health and performance areas. Colloca and Barsky (2020) proposed that in clinical practice, the nocebo response can be reduced by educating the patients about the mechanisms and the entire phenomenon, using communication strategies that minimize negative associations, facilitate the communication between clinicians, and patients. We think that the aforementioned points stand for motor performance too. Thus practitioners (e.g., caregivers, teachers, coaches) should follow these guidelines to minimize nocebo responses in motor performance. This assumption is further supported by the Zech *et al*. (2020) empirical study, where it was shown that in clinical situations, the nocebo effect on muscular strength could be avoided by using alternative communicative formulations instead of ones that evoke negative associations.

CONCLUSION

In this systematic review, we found that the nocebo phenomenon is present in motor performance. Therefore, practitioners in performance-enhancing and health-promoting professions should be conscious of the adverse effects of negative communication and or intervention(s) perceived by the client as harmful. Further research in this area is needed by using between-subjects research design and a no-agent control condition. The risk of bias could be decreased by improving the randomization process and preregistering study design and data analysis.

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