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Delayed effects of attention on pain sensitivity and conditioned pain modulation

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Abstract

Background: Efficacy of pain modulation is assessed as the difference in pain sensitivity during a painful conditioning, compared to before (conditioning pain modulation, CPM). Attention can be assessed with the Stroop task, in which participants report the number of words on a screen; either congruent or incongruent with the value of the words. Attention away from painful stimuli during CPM enhances the CPM effect. However, it is unknown if attention influences CPM effects when the two are done in sequence.

Methods: Healthy men ($n = 25$) underwent cuff algometry CPM-assessment where the pressure-pain detection and tolerance thresholds (PTT) were recorded on one leg with and without contralateral conditioning. Two identical sessions of four test stimuli equal to PTT (5 s, 1-min interval, scored on a visual analogue scale, VAS) with a painful conditioning from the second to the last test-stimulus were performed. Stroop sessions were followed by test stimuli with or without painful conditioning.

Results: The VAS scores in the first two sessions showed excellent reliability (ICC = 0.92). VAS scores were lower in sessions with Stroop compared to sessions without Stroop ($p = .05$) indicating an analgesic effect of Stroop. Participants were subgrouped into CPM responders and CPM non-responders according to CPM effects in the first two sessions. CPM non-responders ($n = 13$) showed facilitation to repeated noxious stimuli in all sessions with no effect of conditioning or Stroop ($p = .02$).

Conclusion: Attention and CPM both modulate pain in healthy men. Attention-induced analgesia works in CPM non-responders. Results indicate that attention and CPM are not the same and that they do not demonstrate additive effects when applied in sequence.

Significance: Pain sensitivity is reduced after an attention task in healthy men. The delayed effects from attention only have minor effects on Conditioned Pain Modulation (CPM), and results support that attention-driven analgesia works independently of CPM. Results indicate that individual strategies for pain inhibition exist and that an overlap between the mechanisms of CPM and selective attention is limited. Moreover, painful phasic stimuli may increase the number of healthy volunteers with negative CPM effects.

1 | INTRODUCTION

The ability to inhibit one pain with another is impaired in some patients (Arendt-Nielsen et al., 2018), and a link to cognition has been suggested (Bushnell, Ceko, & Low, 2013). The pain-inhibits-pain-effect is assessed by conditioned pain modulation (CPM) (Yarnitsky et al., 2015). The reliability of CPM is moderate to excellent (Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016; Petersen, Vaegter, & Arendt-Nielsen, 2017). CPM is not always associated with pain inhibition in healthy participants (Potvin & Marchand, 2016), and non-responders may respond differently to cognitive load. Attention away from pain during CPM has an additive effect on pain inhibition (Moont, Pud, Sprecher, Sharvit, & Yarnitsky, 2010) and the analgesic effect of attention correlates with pain inhibition after controlling for confounders (Oosterman, Dijkerman, Kessels, & Scherder, 2010). Pain inhibition during distraction and CPM are not the same (Lautenbacher, Prager, & Rollman, 2007; Moont, Crispel, Lev, Pud, & Yarnitsky, 2012; Moont et al., 2010). In support of this, CPM effects do not diminish when repeated over 20 minutes (Hoegh, Petersen, & Graven-Nielsen, 2018) while attention-induced analgesia does (Silvestrini & Rainville, 2013). However, some authors suggest that CPM and attention could depend on the capacity of the same descending control systems (MacLeod, 1992; Silvestrini & Rainville, 2013; Stroop, 1935).

The Stroop task (MacLeod, 1992; Stroop, 1935) is an attention-demanding task that may influence endogenous pain modulation for up to 5 minutes (Hamer, Boutcher, & Boutcher, 2003). Stroop has been used to study the role of cognitive load on pain sensitivity (Marouf et al., 2014; Oosterman et al., 2010; Wilder-Smith et al., 2013). Stroop can distract healthy volunteers during experimental pain leading to an analgesic effect (Bantick et al., 2002; Fechir et al., 2009; Martinsen et al., 2014, 2018; Oosterman et al., 2010; Wilder-Smith et al., 2013) but only one out of these studies reported analgesia *after* Stroop (Martinsen et al., 2014).

Painful stimuli do not appear to have any effect on reaction time (Aniskin et al., 2011) or brain activation patterns during Stroop (Seminowicz, Mikulis, & Davis, 2004). Three studies reported correlations between CPM efficacy and shorter reaction time during Stroop in healthy volunteers (Coppieters et al., 2015; Marouf et al., 2014; Meeus et al., 2015). However, one study was based on a small sample size (Meeus et al., 2015), two studies did not find any statistical significant CPM effect (Coppieters et al., 2015; Meeus et al., 2015), and the third study did not find significant correlations between CPM and Stroop (Marouf et al., 2014) questioning the generalizability of results. A fourth study found a positive correlation between pain inhibition during CPM and pain inhibition during Stroop (Wilder-Smith et al., 2013). None of the four studies controlled for the influence of pain on attention or the degree of CPM effects at baseline.

The aim of this study was to assess the difference between conditioned pain and unconditioned pain without or immediately after Stroop task performance. It was hypothesized that pain sensitivity would be reduced immediately after Stroop but that pain would not affect reaction time during Stroop. It was hypothesized that both Stroop and CPM activate descending pathways and therefore that CPM responders have stronger Stroop-induced analgesia than CPM non-responders.

2 | MATERIALS AND METHODS

2.1 | Subjects

Participants were all male and between 18 and 72 years old (mean 30.2 ± 10.8 standard deviation). One participant was 72 and the median age was 28. All were recruited via social media and flyers on and around a university and university college. Exclusion criteria included: a diagnosed sleep, neurological, mental or musculoskeletal disorder; less than 6 hours of sleep within the past 24 hours; any recent lesions to the skin or other tissues in the experimental area; any report of pain, use of sleep medication or pain medication within the last 2 days; any medical diagnosis indicating stress or chronic pain. All participants were informed about the experiment and provide written consent before entering into the study. The study was approved by the local Ethics Committee (N-20170033) and was performed in accordance with the Helsinki Declaration.

2.2 | Experimental protocol

Throughout the study, participants were placed comfortably with back support in a sitting position with legs extended and a small pillow under the knees. A computer screen (15″) was placed slightly off to the left at a distance from which they could comfortably read the text during the Stroop task.

Pain measurements at baseline included bilateral *pain detection thresholds* (PDTs) and *pain tolerance thresholds* (PTTs) and *conditioned pain modulation* (CPM), which were all recorded by cuff pressure algometry on the lower legs (Graven-Nielsen, Izumi, Petersen, & Arendt-Nielsen, 2017) (Figure 1).

To test for reliability of the phasic test stimuli with conditioning (CPM), two sessions were conducted (Pain-I and Pain-II). In these sessions test stimuli were equal to PTT and painful conditioning was applied on the contralateral leg starting with the second test stimulus and continuing until the end of the last test stimulus. Pain-I and Pain-II were also used as controls for the Stroop-pain-conditioning session (see below).

The test stimuli in the three experimental sessions were always preceded by Counting Stroop task (Bush et al., 1998;

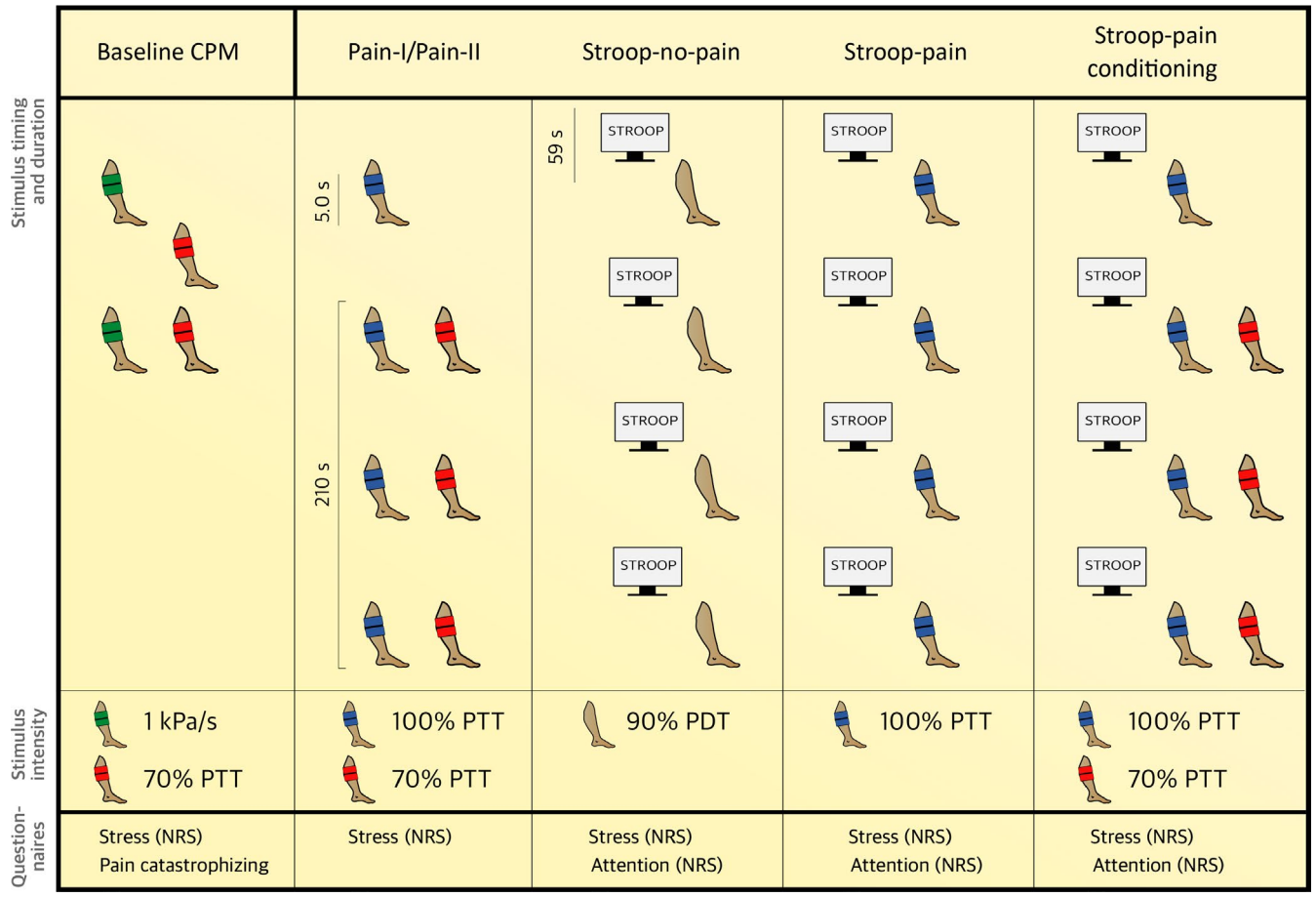

FIGURE 1 Overview over the study and protocol. At baseline CPM, self-perceived stress and Pain Catastrophizing Scale was measured (first column). The sessions without Stroop (Pain-I and Pain-II) were identical and included four phasic (5 s) test stimuli on the dominant leg. The last three test stimuli were conditioned with a tonic (210 s) pressure. Before the test stimuli a break of 1 min was applied. The three Stroop sessions started with a Stroop test (59 s) followed by one of the following: Mild, non-painful pressure (Stroop-no-pain), painful pressure (Stroop-pain) or painful pressure and a parallel, tonic, stimulus on the non-dominant leg during the last three Stroop and pressure stimuli (Stroop-pain-conditioning). After all sessions self-perceived stress was assessed and after all Stroop sessions self-perceived attention was assessed

Seminowicz et al., 2004). This way the participants were not distracted by Stroop during pain or vice versa (Ivanec, Pavin, & Kotzmuth, 2007; Legrain et al., 2012; Moore, Keogh, & Eccleston, 2012). The three sessions were delivered in a randomized order and consisted of test stimuli either equal to 90% of PDT (Stroop-no-pain), to PTT (Stroop-pain), or to PTT with painful conditioning (Stroop-pain-conditioning). In the latter session conditioning was applied on the contralateral leg and tonically maintained from the second through fourth test stimuli. In order to measure the immediate effect of Stroop, a phasic test stimulus paradigm was applied (McPhee & Graven-Nielsen, 2018).

2.3 | Catastrophizing, stress and attention

Pain catastrophizing has been associated with a reduced CPM effect (Traxler, Hanssen, Lautenbacher, Ottawa, & Peters, 2019) and Stroop has sometimes been considered a stress-test (Usui & Nishida, 2017). To control for these factors and to measure the self-perceived attention during Stroop, three self-reported outcomes were collected: *Pain Catastrophizing Scale* (PCS) questionnaire in Danish (Kjøgx et al., 2014) or English (Sullivan, Bishop, & Pivik, 1995), *perceived stress* (Geva, Pruessner, & Defrin, 2014) and *perceived attention* (Maurer & Pierce, 1998). Stress and attention were scored on a numerical rating scales (NRS, 0–10; with 10 being "*maximum stress/attention"* and 0 = "*no stress/attention*"). A total of six stress-ratings were collected: at baseline (prior to any test stimuli), after baseline assessments, after Pain-II and after each of the three Stroop sessions. Subjects also asked to rate their attention towards the Stroop task in the beginning and in the end of each session – i.e. a total of six times in three sessions.

2.4 | Stroop task

The Stroop task was used to increase cognitive load through cognitive inhibition that is the ability to inhibit cognitive

"habits" (i.e. inhibit *the first thing that comes to mind* upon a visual stimulus and follow a strict rule under time pressure) (Stroop, 1935). In the present experiment, the Counting Stroop task (or Number Stroop) (Bush et al., 1998; Seminowicz et al., 2004) was used and participants were asked to count the amount of words on the screen and to report them using a numeric keyboard. The words on the screen (*one, two, three* or *four*) were either congruent with the amount of words (e.g. the word "two" appear twice) or incongruent (e.g. the word "one" appear twice). Accuracy (in percent) as well as reaction time were recorded for analysis (Bush et al., 1998) in ePrime (v3.0; Psychology Software Tools). The participants had the choice of words being in Danish or English (depending on nationality).

Participants were exposed to four 1-min blocks of Counting Stroop in each of the last three sessions (Stroop-no-pain, Stroop-pain, Stroop-pain-conditioning). The Stroop-no-pain session controlled for differences in Stroop reaction time and accuracy as a consequence of pain. Within each block, incongruent and congruent tasks were mixed (Geva et al., 2014; Maurer & Pierce, 1998) to keep participants vigilant as previous studies show correlations between reaction time and pain assessment (Bantick et al., 2002; Oosterman et al., 2010) and between reaction time and assessment of CPM (Meeus et al., 2015). The experimental sessions were different in regards to pressure intensity but identical in terms of Counting Stroop, and the order of the three Stroop sessions was randomized between participants.

2.5 | Cuff algometry

A computer-controlled cuff pressure algometer (NociTech, Denmark, and Aalborg University) was used to assess PDT and PTT (test stimuli) as well as to induce the conditioning stimulus. The computer-controlled air compressor was mounted with two independent 7.5 cm tourniquets (silicone high-pressure cuff; VBM Medizintechnik GmbH) (Graven-Nielsen et al., 2017), an electronic VAS (0–10 cm), and a stop button. Endpoints of the VAS were defined verbally for participants before assessment (0 = "no pain" and 10 cm = "maximal pain"). Participants were instructed on how to use the stop button in case they wanted to terminate cuff inflation and stop the study. The tourniquets were fitted on top of the most voluminous aspect of the triceps surae muscle on the lower legs. The upper and lower borders of the cuff were visually marked on the participant's skin to ensure the cuffs remained in place throughout the experiment. This method has previously been shown to produce reliable measurements of CPM based on PDT and PTT (Graven-Nielsen et al., 2017), with CPM based on PDT providing the most stable and robust CPM effects (Hoegh et al., 2018). Healthy men appear to have more efficient CPM compared to healthy women (Skovbjerg et al., 2017) and thus the current study was performed only in men.

At baseline, PTT and PDT assessments were recorded by inflating the cuff slowly (1 kPa/s) during which subjects scored the perceived pressure-pain intensity in real time on the VAS, until they pressed the stop button (defining PTT). If a participant did not reach PTT before a stimulation intensity of 100 kPa the cuff deflated automatically. For data analysis the cuff pressure equal to perceived pain of 1 out of 10 on the VAS was defined as PDT (Graven-Nielsen et al., 2017).

2.6 | Conditioned Pain Modulation

The baseline CPM assessments were done by repeating the cuff inflation on the dominant leg simultaneously with a tonic painful cuff inflation on the non-dominant leg equal to the PTT level on that leg. The conditioning was stopped when the PPT level was reached on the dominant leg. The CPM effect was calculated as the difference between PDT during conditioning minus PDT without conditioning. A positive CPM effect represents reduced pain sensitivity during conditioning.

2.7 | Phasic test stimulations

The phasic cuff stimulations had rapid onset (100 kPa/s) and lasted for 5 s each. A total of four cuff stimuli were conducted in each session (starting at 62, 127, 191 and 256 s). Before each train of stimuli there was an approximately 1-minute period during which the Stroop task was performed (for Stroop sessions) or where subjects were instructed to rest quietly (for Pain-I and Pain-II sessions). The total duration of a session was approximately 4 min and 20 s and all sessions were separated by 5 min rest to account for accumulating effects (Hoegh et al., 2018). For each test stimulus the peak VAS score was extracted. In the sessions with conditioning on the contralateral leg, the conditioning pain intensity was rated verbally on a NRS (0–10, 10 defined as maximal pain) after each of the four test stimuli.

Participants were subgrouped into "CPM responders" and "CPM non-responders" based on pain VAS scores from phasic test stimuli during the conditioning (average of 2–4th VAS score in Pain-I and Pain-II) subtracted from the unconditioned test stimulus VAS score (average of the 1st stimulus in Pain-I and Pain-II). Participants who experienced more pain during the conditioned test stimuli (2–4th) compared to the unconditioned (1st) were classified as CPM non-responders and participants with no change or reduced pain sensitivity during the conditioned test-stimuli were classified as CPM responders (Potvin & Marchand, 2016).

2.8 | Statistics

Based on pilot studies power calculation indicated that 25 healthy male volunteers was necessary to have a power of 0.8 and an alpha on 0.05 (*SD* 1.5 points on a visual analogue scale, VAS). Data are presented as mean and standard error of the mean (*SEM*) unless otherwise specified. All data but age was normally distributed (visual inspection of Q-Q plot) or log-transformed (log10) to approach normal distribution before statistical analysis. Effect sizes are reported as partial eta squared (η_P^2) and interpreted so that effect sizes above 0.14 are considered large and effect sizes below 0.01 as small (Lakens, 2013).

Stroop reaction time and accuracy were analysed in two-way repeated measures analysis of variance (ANOVA) with factors *congruency* (congruent, incongruent) and *Stroop sessions* (Stroop-no-pain, Stroop-pain, Stroop-pain-conditioning). Spearman correlation was made between an average of congruent and an average of incongruent reaction time and accuracy, respectively, with age. Self-perceived attention scores were analysed in a two-way repeated measures ANOVA with factors *time* (beginning, end) and Stroop sessions. Furthermore, both ANOVAs of Stroop performance (reaction time and accuracy), as well as the ANOVA of attention were analysed with *CPM group* as an additional factor to explore difference between the groups.

Self-perceived *stress* scores before and after Stroop were analysed as an average of the three stress scores without Stroop (baseline, post-baseline, post Pain-II) and an average of the three scores in sessions with Stroop (Stroop-no-pain, Stroop-pain, Stroop-pain-conditioning) in a paired t-test. We also examined the relationship between PCS-scores and stress scores in CPM responders and CPM non-responders, using Pearson correlations.

Interclass Correlation Coefficient (ICC) of VAS -scores from the two identical Pain-I and Pain-II sessions was performed in a form 3,1 (two-way mixed-effect model with consistency) for each pair of test-stimuli with single and average measures and 95% confidence intervals reported (Koo & Li, 2016; Shrout & Fleiss, 1979). ICCs between 0.5 and 0.75 indicate moderate reliability, 0.75–0.90 indicate good reliability and above 0.90 is considered excellent reliability (Koo & Li, 2016).

The baseline CPM measurement was analysed with a paired sample t-test of PDT (conditioned vs. unconditioned test stimulus). The effect of conditioning during Pain-I and Pain-II sessions were analysed in a two-way repeated measures ANOVA with *test stimulus* (1st, average of 2–4th) and *session* (Pain-I, Pain-II).

The difference in VAS scores between conditioned and unconditioned test-stimuli (i.e. CPM effects) within the subgroups (CPM responders and CPM non-responders, respectively), was analysed in paired t-tests. Furthermore, VAS scores were analysed in a three-way repeated measures ANOVA with within-subject factors *test-stimuli* (1st test stimulus, average of 2–4th test-stimuli) and *sessions* ($Pain_{avg}$, Stroop-pain, Stroop-pain-conditioning) and between-subject factor *CPM groups* (CPM responders, CPM non-responders).

An exploratory analysis was made to facilitate further understanding of the difference between CPM responders and CPM non-responders. For this analysis the ΔVAS, i.e. differences in VAS-scores between each of the three sessions ($Pain_{avg}$, Stroop-pain and Stroop-pain-conditioning) were calculated: $Pain_{avg}$ minus Stroop-pain (=CPM-Stroop-effect), $Pain_{avg}$ minus Stroop-pain-conditioning (=Stroop-effect) and Stroop-pain minus Stroop-pain-conditioning (=Stroop-Conditioning-effect). The three delta values were analysed for 1st test stimulus and 2–4th test-stimuli, respectively, in separate two-way repeated measures ANOVA with factors *ΔVAS* (CPM-Stroop-effect, Stroop-effect and Stroop-Conditioning-effect) and *CPM groups* (CPM responders, CPM non-responders).

Correction with Greenhouse-Geisser was applied when sphericity was violated in the ANOVAs. Pairwise deletion was used in case of missing data. Statistical significance was accepted at $p \leq .05$ and post-hoc repeated measures comparisons were corrected by Bonferroni (Bon).

3 | RESULTS

3.1 | Stroop task with and without painful stimuli

In the Stroop task, *reaction time* was slower during incongruent trials compared to congruent (Figure 2a; ANOVA: $F(1, 24) = 48.44$, $p < .0005$, $\eta_P^2 = 0.669$) and no difference was observed between the three Stroop task sessions. There was no significant correlation between age and reaction time or accuracy during Stroop Task. *Accuracy* on the Stroop task was also not different between Stroop sessions and participants were more accurate during the congruent compared to the incongruent tasks (Figure 2b: ANOVA; $F(1, 24) = 43.49$, $p < .0005$, $\eta_P^2 = 0.644$). Self-perceived attention towards the Stroop task was high (7.9 ± 0.2) and there were no interactions or main effects of time or session in the self-perceived attention during Stroop. No interactions were found between any of the outcomes related to Stroop performance and CPM groups. This suggests that the Stroop task was successfully applied without influence of the pain sessions on Stroop task performance.

3.2 | Perceived stress and pain catastrophizing

Self-perceived stress was very low on average (1.5 ± 0.3) throughout the study. *Pain Catastrophizing Scale* (*PCS*) scores were also low on average (7.6 ± 1.1). Stress scores

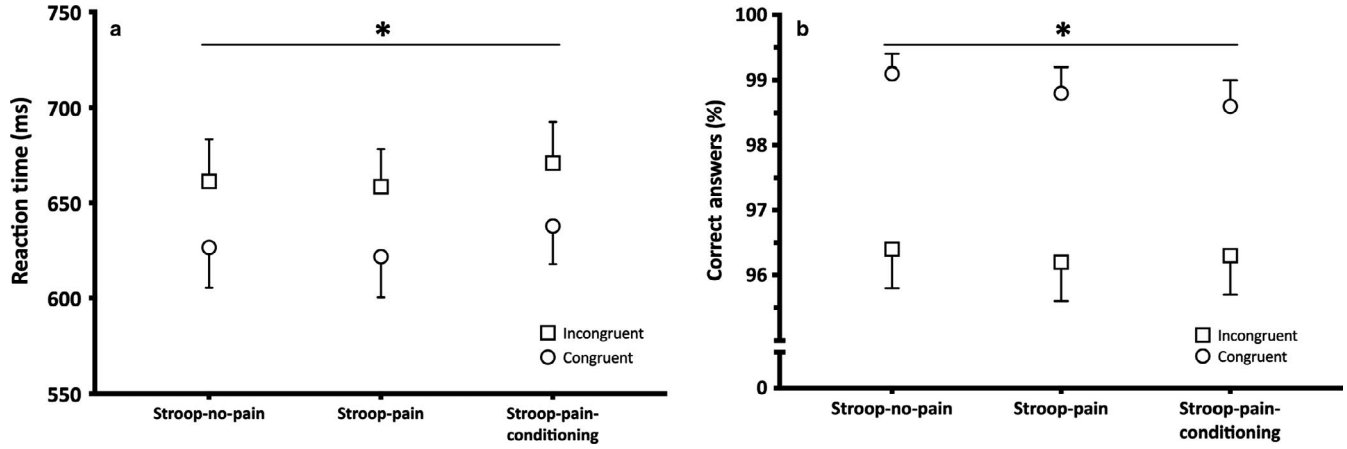

FIGURE 2 Mean (±SEM, $n = 25$) reaction time (a) and correct answers (b) for congruent numbers (circles) and incongruent numbers (squares) in each of the three experimental sessions (Stroop-no-pain, Stroop-pain, Stroop-pain-conditioning). Significant differences between incongruent numbers and congruent numbers are illustrated (*$p < .0005$)

before Stroop and during Stroop sessions were not significantly different and no correlations were found between PCS-scores and stress or CPM response.

3.3 | Perception of cuff test-stimuli

Average VAS scores of the test-stimuli (Table 1) in the five sessions were 6.3 ± 0.3 (Pain-I), 6.1 ± 0.3 (Pain-II), 0.5 ± 0.2 (Stroop-no-pain), 5.3 ± 0.4 (Stroop-pain) and 5.4 ± 0.4 (Stroop-pain-conditioning).

TABLE 1 VAS scores in all sessions

	Stimulus	Mean	SEM
Pain-I	1	6.16	0.34
	2	6.26	0.33
	3	6.33	0.33
	4	6.57	0.31
Pain-II	1	5.59	0.37
	2	6.20	0.33
	3	6.43	0.38
	4	6.41	0.37
Stroop-no-pain	1	0.40	0.19
	2	0.50	0.20
	3	0.54	0.23
	4	0.61	0.21
Stroop-pain	1	5.04	0.39
	2	5.29	0.41
	3	5.50	0.43
	4	5.25	0.47
Stroop-pain-conditioning	1	5.16	0.36
	2	5.50	0.44
	3	5.62	0.40
	4	5.46	0.52

Note: Average and SEM ($N = 25$) of visual analogue scale (VAS) scores of cuff test-stimuli in the five sessions.

3.4 | Cuff test-stimuli shows excellent reliability

Data from one person were missing in the first session (4th test stimulus, Pain-I) and consequently data from this person was excluded in the other session (4th test stimulus, Pain-II). A total of 99 data sets from 25 people in four sessions were used to calculate reliability.

The overall test-retest reliability between VAS scores in Pain-I and Pain-II sessions showed excellent reliability (ICC = 0.96 (95% confidence interval: 0.93–0.98, $F(7, 161) = 2.86$, $p = .008$) for the average VAS score across the four test-stimuli. The reliability of the first, unconditioned test stimulus was defined as good (Figure 3; ICC = 0.83, 95% confidence interval: 0.61–0.92, $F(1, 24)$, $p < .0005$) and the reliability for an average of 2–4th test-stimuli was excellent (Figure 3; ICC = 0.92, 95% confidence interval: 0.82–0.97, $F(1, 24)$, $p < .0005$). See Table 2 for individual ICC.

3.5 | Conditioned pain modulation

The intensity of the conditioning stimulus was 47.3 ± 14.8 kPa throughout baseline and experimental sessions. There was a positive CPM effect at baseline, with an PDT during conditioning (38.7 ± 3.4 kPa) significantly greater than PDT before conditioning (31.7 ± 2.3 kPa; $t(24) = -4.14$, $p < .0005$).

There was no significance difference between Pain-I and Pain-II sessions of VAS scores in the conditioned (2–4th) test-stimuli compared to the unconditioned (1st) test-stimulus (ANOVA: $F(1, 24) = 3.63$, $p = .07$, $\eta_P^2 = 0.131$). However, an interaction between *test stimulus* and *session* (ANOVA: $F(1,$

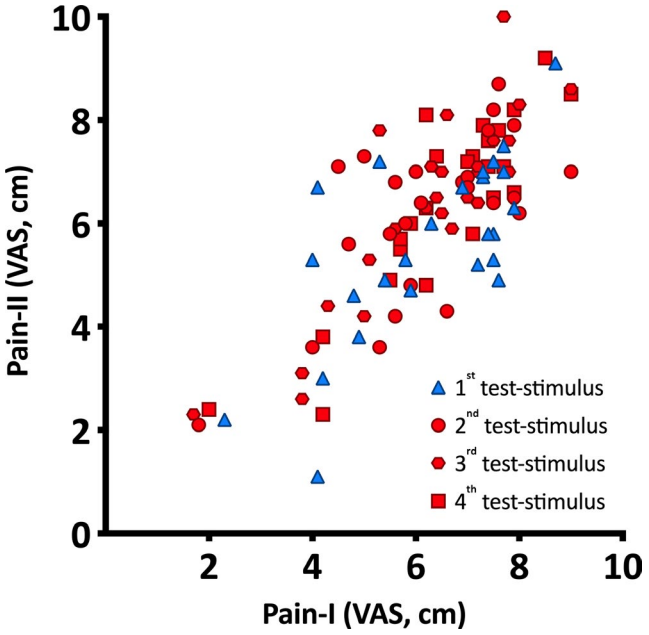

FIGURE 3 Scatter-plot of VAS scores of test-stimuli in the Pain-I and Pain-II sessions. The two unconditioned test stimuli showed good reliability (Triangles: ICC = 0.83, 95% CI: 0.61-0.92). The second (circles), third (hexagon) and fourth (squares) test stimuli showed excellent reliability (ICC = 0.92, 95% CI: 0.82-0.97). CI, Confidence Interval; ICC, Interclass Correlation Coefficient

24) = 4.80, $p = .04$, $\eta_P^2 = 0.167$) allowed for post-hoc analysis, which showed that VAS scores were lower during the 1st test stimulus in the Pain-II session compared to Pain-I (Bon: $p = .02$). No significant differences were found between the conditioned and unconditioned test-stimuli in the Pain-I session, but an increase in VAS scores from the 1st to the 2–4th test-stimuli was found in the Pain-II session (Bon: $p = .02$), as an indication of a negative CPM effect in the Pain-II session. This led to an exploratory analysis of CPM responders and CPM non-responders on averaged Pain-I and Pain-II ($Pain_{avg}$).

Based on $Pain_{avg}$ (i.e. VAS scores without Stroop) 13 participants had increased VAS scores during conditioning and were considered *CPM non-responders* and 12 participants were considered *CPM responders*. Within-group analysis showed that PDT decreased from 6.0 ± 0.5 to 5.5 ± 0.5 cm on the VAS ($t(11) = -3.80$, $p = .03$) for *CPM responders*, while the CPM non-responders showed facilitation during conditioning from 5.8 ± 0.4 to 7.0 ± 0.2 cm on the VAS ($t(12) = 4.10$, $p = .001$).

3.6 | Pain is inhibited after Stroop

A three-way ANOVA of VAS scores for test-stimuli across the sessions and groups revealed an interaction between *CPM groups* and *time* (Figure 4; ANOVA: $F(1, 23) = 15.84$, $p = .001$, $\eta_P^2 = 0.408$) and a main effects for *session* (ANOVA; $F(2, 46) = 5.56$, $p = .007$, $\eta_P^2 = 0.195$) and *time* (ANOVA; $F(1, 23) = 4.85$, $p = .04$, $\eta_P^2 = 0.174$). Main effects showed that VAS scores were higher during $Pain_{avg}$ when compared to each of the Stroop sessions (Bon: $p \leq .05$). A post-hoc analysis of the interaction showed that the *CPM non-responders* showed facilitation during the 2–4th test-stimuli (Figure 4; Bon: $p < .0005$) compared with the 1st test stimulus.

3.7 | The differences between sessions and CPM groups

The difference in the VAS scores between the three sessions (CPM-Stroop-effect, Stroop-effect and Stroop-Conditioning-effect) showed a week trend towards a difference during the 1st test stimulus (Figure 5a; ANOVA: $F(1.3, 31.3) = 3.13$, $p = .08$, $\eta_P^2 = 0.120$) and no interaction between sessions and CPM groups was found. However, a difference was found between sessions during the 2–4th test-stimuli (Figure 5b; ANOVA: $F(1.3, 31.0) = 5.45$, $p = .02$, $\eta_P^2 = 0.193$). Pairwise comparisons showed that the change in VAS was lower in *Stroop-Conditioning-effect* compared to *Stroop-effect* (Bon: $p = .02$) but not to *CPM-Stroop-effect*.

4 | DISCUSSION

This study explored the influence of a non-sensory (attention) task on pain-induced analgesia (i.e. CPM), and it shows

TABLE 2 Test-retest reliability of repeated test-stimuli in the first two sessions (Pain-I, Pain-II)

	ICC	95% Confidence intervals		ICC	95% Confidence intervals	
	Single measures	Lower bound	Upper bound	Average measures	Lower bound	Upper bound
1st test stimulus	0.705	0.436	0.858	0.827	0.607	0.924
2nd test stimulus	0.672	0.384	0.841	0.804	0.554	0.913
3rd test stimulus	0.864	0.715	0.938	0.927	0.834	0.968
4th test stimulus	0.873	0.728	0.943	0.932	0.843	0.971
Average of 2–4th	0.852	0.693	0.932	0.920	0.818	0.965

Note: Intraclass Correlation Coefficients (ICC) and 95% confidence intervals of the four stimuli (1–4th) as well as for the average of the three conditioned (2–4th) stimuli in the two Pain-only sessions (Pain-I, Pain-II).

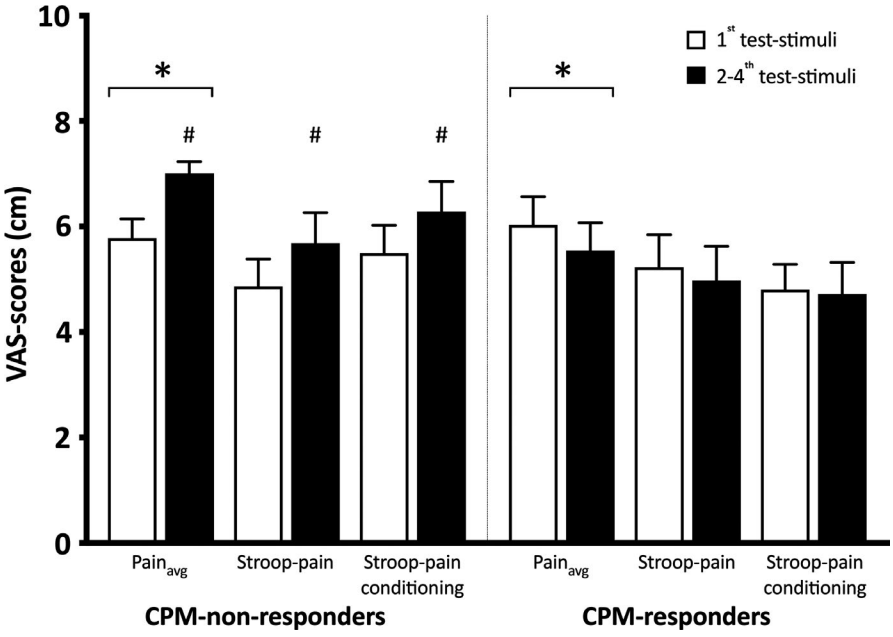

FIGURE 4 Mean (+SEM) pain VAS scores for the 1st and 2–4th test-stimuli, respectively are shown for each of the three sessions ($Pain_{avg}$, Stroop-pain and Stroop-pain-conditioning) and for CPM non-responders and CPM responders. VAS scores were higher during $Pain_{avg}$ compared to the Stroop-pain-sessions (*Bon: $p \leq .05$) and during the 2–4th test-stimuli compared with the 1st test stimulus for CPM non-responders ($^{\#}$Bon: $p < .0005$)

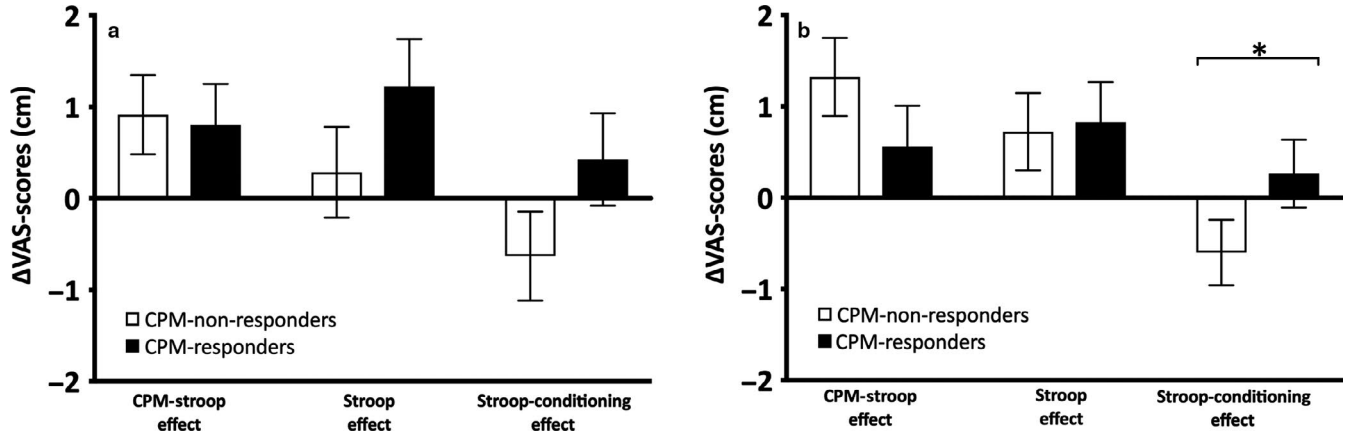

FIGURE 5 Mean (±SEM) difference in VAS scores (ΔVAS) between the three sessions for CPM non-responders and CPM responders during the 1st test stimulus (a) and the 2–4th test-stimuli (b). The "Stroop-Conditioning-effect" was lower than "Stroop effect" (*Bon: $p = .02$)

that Stroop (attention) does not significantly influence CPM. Nonetheless, Stroop inhibited pain in healthy men for up to 1 minute after the attention task has ended. Despite this the analgesic effects of Stroop, it was not able to transform CPM non-responders into CPM responders. Instead, results show that Stroop has an effect on both CPM responders and CPM non-responders, providing a strong indication for different mechanisms.

4.1 | Attention manipulation

Participants reported a high degree of attention during the Stroop task but there were no differences between reaction time or accuracy on the task in the three sessions (Stroop-no-pain, Stroop-pain, Stroop-pain-conditioning), indicating that Stroop performance was unaffected by the painful test-stimuli in this study, which is in accordance with the hypothesis. These results are supported by existing evidence from brain imaging research, which also find minimal influence of pain on brain activation patterns during Stroop task (Seminowicz & Davis, 2007a; Seminowicz et al., 2004) or differences in Stroop performance during pain compared to without pain (Aniskin et al., 2011; Seminowicz & Davis, 2007b). Moreover, the reaction time and accuracy were comparable to previous studies (Seminowicz et al., 2004). Furthermore, the results in this study support a comprehensive study on the influence of pain on different aspects of attention, which conclude that pain has no influence on selective attention using a conflict task comparable to the Stroop task (Moore et al., 2012).

4.2 | Stress and catastrophizing

In the current study, perceived stress was very low (<2/10) and thus changes during the study were minimal (<0.5 out of 10) (Jaeschke, Singer, & Guyatt, 1989; Ries, 2005; Tashjian,

Deloach, Porucznik, & Powell, 2009). This clearly shows that participants did not perceive Stroop nor the painful stimulations to be stressful.

The mean PCS-scores (7.6 ± 1.1) were lower than expected in healthy volunteers (Kjøgx et al., 2014) indicating that none of the participants had maladaptive coping strategies involving rumination, magnification or helplessness. Also, PCS-scores did not correlate with stress or CPM measures indicating that these factors did not confound the results.

4.3 | The effect of Stroop task on pain intensity

In accordance with the hypothesis, the results show that VAS scores were lower during Stroop sessions compared to sessions with stimulus-evoked pain without Stroop and with no differences between Stroop-pain and Stroop-pain-conditioning. These results support top-down analgesia possibly derived via cortical and/or subcortical regions (Damien, Colloca, Bellei-Rodriguez, & Marchand, 2018; Wiech, 2016), and align with the existing literature showing that Stroop is sufficient to reduce pain sensitivity in healthy participants (Bantick et al., 2002; Fechir et al., 2009; Martinsen et al., 2014, 2018; Oosterman et al., 2010; Wilder-Smith et al., 2013) although one study found increased pain with increased cognitive load (Silvestrini & Rainville, 2013) and no significant difference in pain sensitivity was found in another study (Aniskin et al., 2011). Of previous studies only three looked at differences between congruent and incongruent paradigms with regards to pain sensitivity (Bantick et al., 2002; Martinsen et al., 2014, 2018) and a difference was only found in one of the three (Bantick et al., 2002). However, Bantick et al. (2002) used retrospective pain reports, which is likely to have affected the results (Pincus, Fraser, & Pearce, 1998). Thus, attention rather than e.g. cognitive load appear to be related to the hypoalgesic effect of Stroop task. Moont et al. (2010) also found no difference in analgesic effects between different levels of cognitive load when attention is applied in parallel with the painful stimulus (i.e. distraction) (Moont et al., 2010).

4.4 | Conditioning pain modulation

In line with a large body of evidence, this study showed pain reduction during conditioning pain modulation at group-level based on a cuff algometry CPM paradigm at baseline (Graven-Nielsen et al., 2017; Hoegh et al., 2018; Kennedy et al., 2016; Petersen et al., 2017). The phasic cuff test-stimuli paradigm (5 s pressure stimulations) showed excellent reliability. VAS scores during the 1st test stimulus were lower in Pain-II compared to Pain-I. It is unlikely that the difference between Pain-I and Pain-II VAS- scores are related to carry-over effects because they were separated by a 5-min break, which has previously been found to be sufficient to reduce the risk of carry-over effects (Graven-Nielsen et al., 2017; Hoegh et al., 2018; Imai, Petersen, Mørch, & Arendt-Nielsen, 2016; McPhee & Graven-Nielsen, 2018), was included between the two sessions. Two recent studies have used phasic test-stimuli (Lie et al., 2017; McPhee & Graven-Nielsen, 2018) of which one does not find CPM effects (McPhee & Graven-Nielsen, 2018) while the other study does show a CPM effect (Lie et al., 2017). More studies indicate that the duration of a conditioning stimulus is less important for CPM effects than the intensity of the stimulus (Graven-Nielsen et al., 2017; Smith & Pedler, 2017), however, Lie et al. (2017) show that phasic heat stimuli can induce a CPM effect but that it is smaller compared to a tonic test stimulus. It may be possible that shorter stimulation time in the phasic paradigm is an essential factor in these findings and that longer, phasic test-stimuli may be preferable to shorter phasic test-stimuli.

4.5 | CPM responders compared to CPM non-responders before and after Stroop

It was expected that CPM responders would benefit more than CPM non-responders from Stroop-induced analgesia, but the results did not support this.

About 20% of healthy volunteers show no response or pain facilitation during traditional CPM paradigms (Klyne, Moseley, Sterling, Barbe, & Hodges, 2018; Potvin & Marchand, 2016; Skovbjerg et al., 2017), and it has been suggested that subgroup analysis may provide a better understanding of underlying differences between these groups (Potvin & Marchand, 2016; Vaegter & Graven-Nielsen, 2016). A recent study indicated that reliability of CPM-based subgroups could be modality-dependent with computerized cuff algometry as a reliable method (Vaegter, Petersen, Mørch, Imai, & Arendt-Nielsen, 2018). In the current study, half of the participants ($n = 13$) were classified as CPM non-responders, while the other half ($n = 12$) were CPM responders (Klyne, Schmid, Moseley, Sterling, & Hodges, 2015). The number of CPM non-responders were higher in the phasic test-stimuli paradigm compared to what would be expected (Klyne et al., 2018; Potvin & Marchand, 2016; Skovbjerg et al., 2017). However, the results in the current study are in line with two other studies using comparable paradigms (Lie et al., 2017; McPhee & Graven-Nielsen, 2018). Compared to the classical paradigm with tonic conditioning, the phasic paradigm seem so show a higher number of CPM non-responders, which may reflect inter-individual differences in combination with relatively smaller effects. By definition, CPM responders showed a positive CPM effect and CPM non-responders showed negative CPM effects (i.e. pain facilitation). Most interestingly, the facilitated pain response

in the group of CPM non-responders was significant during repeated, unconditioned test-stimuli as well as to conditioned test-stimuli with and without Stroop, indicating a stable trait of pain facilitation. However, compared to sessions without Stroop, pain after Stroop was reduced both in the presence and absence of a conditioning stimulus for both groups, indicating an effect of cognitive load on pain sensitivity, which appear to exist separately from a CPM effect.

Repeated test-stimuli with and without conditioning has previously been suggested to be a novel method to assess changes in pain sensitivity (Hoegh et al., 2018). Particularly, the net CPM effect (i.e. the difference between the effect of repeated conditioned and repeated unconditioned test-stimuli) is interesting since it may provide novel insights to the balance between facilitative and inhibitory descending control systems (Arendt-Nielsen et al., 2018; Groves & Thompson, 1970; Hoegh et al., 2018). Accordingly, an exploratory analysis of the changes between the sessions (ΔVAS) was conducted for the 1st and the 2–4th test-stimuli, respectively. The analysis showed that *Stroop-Conditioning-effect* was smaller during the 2–4th test-stimuli compared to *Stroop-effect* (Figure 5b), meaning that the net-effect of Stroop alone was higher than the combined effect of Stroop and conditioning. Unlike Moont et al. (2010) who found that distraction (i.e. attention away from a parallel, painful stimulus) has an additive effect on CPM (Moont et al., 2010), the current study finds that when the attention task is done before CPM there is no additive effect in CPM responders. However, the present results support that Stroop is related to analgesia and suggest that Stroop has analgesic effects even in CPM non-responders and therefore that a lack of CPM response to painful conditioning could be modified by a preceding attention task. Hamer et al. (2003) found that blood flow in the forearm was significantly increased during Stroop and they speculated that this could related to descending endogenous effects, however, if such an effect is present during Stroop results from this study suggests that they are insufficient to have an additive effect on CPM after Stroop (Hamer et al., 2003). Together these results support the existing literature speculating that cognitive analgesia and CPM are not the same (Lautenbacher et al., 2007; Moont et al., 2010, 2012) and adds that the timing of the attention task could be critical for additive effects.

4.6 | Top-down, bottom-up or both?

It has been suggested that attention is a *top-down* modulation of pain while sensory stimuli are *bottom-up* modulators (Hauck, Lorenz, Domnick, Gerloff, & Engel, 2015). The painful conditioning stimulus in this study can be categorized as a bottom-up process since it is stimulus-driven, albeit there is agreement that it involves descending pathways (Yarnitsky et al., 2010). The Stroop task, on the other hand, could be considered a *top-down* process since it is initiated by voluntary and goal-oriented attention (Katsuki & Constantinidis, 2014). Brain imaging show that some participants were more likely to attend to Stroop task (during pain) while others were more likely to attend to the pain-stimulus (during Stroop) (Seminowicz et al., 2004) posing that individual differences could involve differences in brain activity. Furthermore, attention analgesia is likely to involve the same subcortical structures as CPM (Erpelding & Davis, 2013; Kucyi, Salomons, & Davis, 2013). From a mechanism-based perspective it could seem that top-down modulation is activated by default under cognitive load (Bantick et al., 2002; Fechir et al., 2009; Martinsen et al., 2014, 2018; Oosterman et al., 2010; Wilder-Smith et al., 2013), and that bottom-up mechanisms can be supplemented by top-down modulation during parallel but not serial application of attention-demanding tasks (Lautenbacher et al., 2007; Moont et al., 2010; Nir, Yarnitsky, Honigman, & Granot, 2012).

Stroop task measures *inhibition* of cognition but other test, such as *n*-back test for working memory (*updating*), may have different effects on pain inhibition and could be relevant to test in a similar paradigm. Expectation is another big top-down modulator of pain (Bjørkedal & Flaten, 2012; Colloca, Corsi, & Fiorio, 2018), however, Stroop-pain and Stroop-pain-conditioning sessions were only different with regards to the conditioning stimulus, so expectations are unlikely to explain the results in this study (Bjørkedal & Flaten, 2012; Nir et al., 2012).

In summary, attention (*top-down*) was key to reducing pain sensitivity in healthy men and responses to painful conditioning (*bottom-up*) may be more dependent on individual variability. In this context, results from this study could be considered exploratory evidence of a spectrum of *bottom-up* and *top-down* triggers working on associated mechanisms in healthy volunteers. Future studies could explore if individual differences in top-down and bottom-up modulation of pain could direct more efficient treatment to clinical populations.

4.7 | Limitations

The results in this study are exploratory in their nature and serve mainly as proof-of-concept for studying the role of attention on pain in an experimental setting. The age span among the participants was very large but it is unlikely that this could have affected the results. Although not compared directly, the paradigms used to test for CPM effects at baseline and during the experimental sessions were not identical and might have imposed a difference in perception of pressure pain in the two paradigms. Phasic cuff pressure test-stimuli may associate with smaller CPM effects than tonic or ramping test-stimuli (Lie et al., 2017) but it was the only feasible paradigm available for

testing deep tissue pain sensitivity in the breaks between the Stroop-trials. However, since no accumulating effect of Stroop (e.g. cognitive exhaustion) was measured, future studies could consider using longer lasting test-stimuli and possibly reach more pronounced CPM effects. This study included a baseline test with a "normal" CPM-paradigm as well as the test-retest reliability of the peak-stimulus paradigm, which also serves as a methodological strength. It allowed test-retest reliability calculations on the same group of participants, as well as direct comparison between conditioned test-stimuli with and without Stroop task. The sample size for this study was sufficient to study changes in CPM effects at group level, not subgroup level, which must be considered when interpreting these results. Also, future studies might consider to use k-means clustering to determine subgroups.

5 | CONCLUSION

This study is the first to measure the delayed effects of Stroop on pain sensitivity in healthy men and to show that Stroop can induce analgesia in participants who show facilitation during CPM. Stroop-induced analgesia does not seem to have an additive effect on CPM. This study concludes that attention-driven analgesia utilizes different or only partially overlapping mechanisms as those of pain-driven analgesia (CPM). Clinically, this could be suggest that that attention-driven analgesia is relevant independently of pain-induced analgesia.

AUTHOR CONTRIBUTIONS

All authors contributed in the study design and planning. MH and TGN analysed data from the cuff and DAS analysed data from the Stroop task. All authors contributed to interpretation of the data and to the finalizing of the manuscript.

CONFLICTS OF INTEREST

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