Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways

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BACKGROUND: Conditioned pain modulation paradigms are often used to assess the diffuse noxious inhibitory control (DNIC) system. DNICs provide one of the main supraspinal pain inhibitory pathways and are impaired in several chronic pain populations. Only one previous study has examined the psychometric properties of the conditioned pain modulation technique and this study did not evaluate intersession reliability.

OBJECTIVES: To evaluate and compare the intra- and intersession reliability of two conditioned pain modulation paradigms using different conditioning stimuli, and to determine the time course of conditioned pain inhibition following stimulus removal.

METHODS: An electronic pressure transducer was used to determine the pressure-pain threshold at the knee during painful conditioning of the opposite hand using the ischemic arm test and the cold pressor test. Assessments were completed twice on one day and repeated once approximately three days later.

RESULTS: The two conditioning stimuli resulted in a similar increase in the pressure-pain threshold at the knee, reflecting presumed activation of the DNIC system. Intrasession intraclass correlation coefficients for the cold pressor (0.85) and ischemic arm tests (0.75) were excellent. The intersession intraclass correlation coefficient for the cold pressor test was good (0.66) but was poor for the ischemic arm test (−0.4). Inhibition of the pressure-pain threshold remained significant at 10 min following conditioning, but returned to baseline by 15 min.

CONCLUSIONS: Within-session reliability of DNIC assessment using conditioned pain modulation paradigms was excellent, but the applicability of assessing pain modulation over multiple sessions was influenced by the conditioning stimulus. The cold pressor test was the superior technique.

Key Words: Diffuse noxious inhibitory control; Pain; Reliability

The efficacy of the DNIC system is commonly measured in a laboratory setting by the conditioned pain modulation paradigm. This technique involves simultaneously applying two painful stimuli over distant regions of the body and assessing how much one (the conditioning stimulus) reduces the pain response evoked by the other (the test stimulus) (9). Because of the noxious requirement of the conditioning stimulus, it is presumed that the physiological mechanism underlying inhibition of the test stimulus involves the DNIC system. Conditioned pain modulation has been evaluated in this manner using a range of conditioning and test stimuli, including thermal (heat or cold), electrical, ischemic, mechanical and chemical stimuli (9). The inhibitory effects of conditioning are maximal during application of the conditioning stimulus and persist for several minutes after termination (10,11), although the precise duration of inhibition is currently uncertain. Some reports have indicated that pain threshold returns to baseline within 5 min of stimulus cessation (4,10-13) while others have reported effects lasting beyond 5 min poststimulus (14,15). Some of the discrepancy between studies is likely to arise from the different

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conditioning and test stimuli that have been adopted, whether stimu-
lus termination is defined as removal of the conditioning stimulus or
when the conditioning pain has returned to zero, and the time interval
that the assessments encompass. Indeed, it has been recently suggested
that the procedures used to assess the efficacy of the DNIC system are
standardized to enable easier comparison between studies (9).

The reliability of the conditioned pain modulation paradigm is also
important to establish so that the significance of changes in DNIC effi-
cacy over time or differences between populations can be evaluated.
One previous study (16) investigated intra session reliability of condi-
tioned pain modulation and reported intraclass correlation coefficients
(ICCs) that are considered fair-good according to standards indicated by
Fleiss (17), although the associated CIs were not reported. In their study,
Cathcart et al (16) used a manual pressure algometer to assess pressure-
pain threshold at the finger and shoulder during painful occlusion of the
opposite arm. No study has currently reported the reliability of the con-
tioned pain modulation paradigm using an automated electronic pres-
sure algometer, which may improve the consistency of threshold
determination, or examined inter session reliability across days. The
aims of the present study were to examine the intra- and inter session
reliability of assessing DNIC function using a standardized assessment
of pressure-pain threshold and the conditioned pain modulation para-
digm; and to provide a detailed examination of the time course of con-
tioned pain inhibition after removal of the conditioning stimulus.

METHODS

Participants

Twenty healthy adults (mean ±SD age 25±8 years, seven male) vol-
unteered to participate in the study. Participants were excluded based
on the following criteria: chronic pain in any part of the body or cur-
rent pain in the lower limbs or back; a pathology affecting sensory
perception; severe heart disease or respiratory conditions; current
medication use (except for the oral contraceptive pill); or inability to
provide informed consent and follow instructions of the study. The
procedures conformed to the guidelines on pain research published by
the International Association for the Study of Pain and were approved
by the local ethics committee. Informed written consent was obtained
from all participants.

Pressure-pain threshold

A custom-built, motor-driven electronic pressure transducer was used
to assess pressure-pain threshold. Participants were positioned in long
sitting on a height adjustable plinth with their right knee at 90° flex-
ion (Figure 1). The pressure probe had a diameter of 12 mm to activate
primarily deep tissue nociceptors (18). It was positioned over the med-
ial joint line of the right knee, 7.5 cm from the center of the patella
tendon. During threshold determination, the probe was pressed into
the knee at a rate of 20 N/s. Participants were provided with a numeri-
ical pain scale from 0 to 100 with the anchors of 0 = no sensation, 25
= discomfort, 50 = pain, 75 = intense pain, and 100 = maximum toler-
able pain (19). They were instructed to press a stop button immedi-
ately when they felt the stimulus had become just noticeably painful (a
score of 50 on the pain scale). At each assessment of the pressure-pain
threshold, two measurements were made approximately 30 s to 45 s
apart, and the average of the two was determined as the threshold.

Conditioning stimuli

Two separate conditioning stimuli were used in the conditioned pain
procedure. The order of conditioning stimuli was randomly assigned
for the first session and remained the same for the second session. The
ischemic arm test involved the placement of an inflatable cuff (14.5 cm)
on the left arm just proximal to the cubital fossa. Participants com-
pleted 2 min of handgrip exercises before elevating their arm for 15 s
(14). Immediately following this movement, the cuff was inflated to
240 mmHg and the arm returned to the horizontal position for 2 min.
The pressure-pain threshold at the knee was assessed at 45 s and 90 s
after cuff inflation.

The cold pressor test involved a water bath that was maintained at
12±1°C. Participants immersed their left hand in the water bath up to
the wrist crease for a period of 2 min. The pressure-pain threshold at
the knee was assessed at 45 s and 90 s after immersing the hand.

RESULTS

Reliability of assessing pain inhibition

At the second session, the same measures described above were
assessed once (measurement C) to establish the inter session reliabil-
ity. Additionally, to examine the time course of conditioned pain
inhibition, the pressure-pain threshold at the knee was obtained at 1, 5,
10 and 15 min following the termination of each conditioning stimu-
lus (n=19). To minimize circadian variations of pain regulation, testing
was conducted at the same time of day for the two sessions. Participants
were also asked to refrain from consuming caffeine, alcohol and nicotine
and undertaking strenuous exercise for a period of 4 h before each
session.

Statistical analysis

To evaluate the efficacy of the DNIC system, the difference in the
pressure-pain threshold between baseline and noxious conditioning
was determined, in which a positive change indicated an increase in
threshold. The intra session (measurement A and B) and inter session
(measurement A and C) reliability of knee pressure-pain threshold,
conditioned pain inhibition and the numerical pain rating of each
conditioning stimulus were evaluated using the ICC. ICC analyses
were conducted using a two-way, mixed effects model with terms of
absolute agreement (20). To examine the time course of inhibition,
pressure-pain thresholds were analyzed using a one-way repeated mea-
sures ANOVA with the factor of time (baseline, during conditioning,
1, 5, 10, 15 min postconditioning). A Huynh-Fedlt correction was used
to adjust for the multiple comparisons. Paired t tests were used to
compare threshold values during and following conditioning to baseline
if a significant ANOVA effect was found. The associated experiment-
wise error rate was also determined (21). The error rate indicated the
percentage of results identified as statistically significant that were
likely to be type I errors. All statistical analyses were conducted using
SPSS version17 (IBM Corporation, USA). Data are presented as
mean ± SD.

Reliability of assessing pressure-pain threshold

Across the three measurements, pressure-pain threshold at the knee
averaged 47±14 N. Table 1 shows the pressure-pain thresholds for
measurements A, B and C and the intra- and inter session ICC reliabil-
ity statistics. The intra session ICC value indicated an excellent
level of reliability while the inter session value was good (17).

Reliability of assessing conditioned pain modulation

Knee pressure-pain thresholds were substantially increased during the
conditioning stimuli, reflecting an increase in pain tolerance at the
right knee during painful stimulation of the left hand. Table 1 shows
the difference in pressure-pain threshold at the three measurement
points as well as the intra- and inter session ICC statistics.
Figure 1) Diagram of the experimental set up. The participant was positioned in long-sitting with the right knee at 90° flexion. A 12 mm diameter probe attached to the pressure transducer was positioned over the medial joint line of the knee. The probe exerted pressure onto the knee at a constant rate until the participant hit the ‘stop’ button, indicating the experience of pain.

Figure 2) Schematic of the experimental protocol. On day 1, both conditioning stimuli were assessed twice, 15 min apart. On day 2, approximately three days later, the two conditioning stimuli were assessed once. The time course of conditioning was also evaluated on day 2 by assessing pressure pain threshold (PPT) at 1, 5, 10 and 15 min postconditioning. CS Conditioning stimuli

Table 1 also shows the average pain scale rating for the two conditioning stimuli at each measurement point. Both conditioning stimuli produced a subjectively painful sensation with an average numerical pain scale score of 62±19 and 73±18 out of 100 for the ischemic arm and cold pressor tests, respectively. The lower bounds of the 95% CIs of these pain ratings were above 50 for both conditioning stimuli, indicating that the conditioning stimuli were indeed painful. The cold pressor test elicited significantly higher ratings on the pain scale compared with the ischemic arm test (P=0.003). The pain scale ratings for the ischemic arm test had fair-good intrasession and excellent intersession reliability. The pain scale ratings for the cold pressor test had excellent intra- and intersession reliability.

The relationship between numerical pain scale ratings and the extent of conditioned pain inhibition was also examined. Using the combined data from the three sessions for both conditioning stimuli, Pearson correlation analysis did not reveal any relationship between the subjective pain rating during conditioning and the change in pressure-pain threshold (r=0).

Time course of conditioned pain inhibition

Figure 3 shows the knee pressure-pain threshold during and following the two conditioning stimuli. The ANOVA revealed a significant effect of time for both the ischemic arm test (F[5, 90]=4.6; P=0.001) and the cold pressor test (F[5, 90]=3.3; P=0.025). For the ischemic arm test the pressure-pain threshold was significantly higher than baseline during conditioning (P<0.001) and at 1 min (P=0.015) and 10 min (P=0.026) following termination of the stimulus (experiment-wise error rate = 8%). There was no significant difference at 5 min (P=0.2) and 15 min (P=0.07). For the cold pressor test, the pressure-pain threshold was significantly higher than baseline during conditioning (P=0.001) and at 1 min (P=0.002), 5 min (P=0.027) and 10 min (P=0.023) following termination of the stimulus (experiment-wise error rate = 6%). There was no significant difference at 15 min (P=0.75).

DISCUSSION

The primary aim of the present study was to determine the reliability of using the conditioned pain modulation paradigm to assess DNIC function in a group of healthy participants. Establishing the reliability of a measure provides an indication of whether the measure is sufficient to identify differences between populations or in the same population over time. Overall, our conditioned pain modulation paradigm

**TABLE 1** Measurement A, B and C, and intra- and intersession reliability data

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Intrasession ICC (95% CI)</th>
<th>Intersession ICC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee PPT (N)</td>
<td>51±15</td>
<td>46±14</td>
<td>42±12</td>
<td>0.87 (0.60–0.95)</td>
<td>0.65 (0.05–0.87)</td>
</tr>
<tr>
<td>Ischemic arm test change (N)</td>
<td>18±11</td>
<td>12±13</td>
<td>10±9</td>
<td>0.75 (0.35–0.90)</td>
<td>−0.4 (−1.8–0.4)</td>
</tr>
<tr>
<td>Cold pressor test change (N)</td>
<td>12±16</td>
<td>10±17</td>
<td>11±10</td>
<td>0.85 (0.62–0.94)</td>
<td>0.66 (0.12–0.87)</td>
</tr>
<tr>
<td>Ischemic arm test pain (NPS)</td>
<td>65±21</td>
<td>60±17</td>
<td>63±21</td>
<td>0.60 (0.24–0.82)</td>
<td>0.82 (0.59–0.92)</td>
</tr>
<tr>
<td>Cold pressor test pain (NPS)</td>
<td>74±20</td>
<td>71±19</td>
<td>73±16</td>
<td>0.94 (0.86–0.98)</td>
<td>0.80 (0.56–0.92)</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise indicated. ICC Intraclass correlation coefficient; NPS Numerical pain scale; PPT Pressure-pain threshold.

*Statistically significant difference (P<0.05) from baseline pressure-pain threshold.
exhibited excellent intrasession reliability; however, intersession reliability statistics were markedly different between the two conditioning stimuli, even though both gave rise to a similar change in the pressure-pain threshold. Intersession reliability using the cold pressor test was fair-good, but the same statistic for the ischemic arm test was poor, questioning the ability of the latter conditioning stimulus to compare conditioned pain modulation across multiple testing sessions. For this reason, we recommend use of the cold pressor test in the future evaluation of DNIC pathways. The cold pressor test generates a more focal type of pain compared with the diffuse effects of ischemia, and this may contribute to its more consistent activation of descending inhibitory pathways.

Only one previous study has examined the intrasession reliability of the conditioned pain modulation paradigm and, to our knowledge, none has reported the intersession reliability. Our intrasession reliability measures were markedly higher than that reported by Cathcart et al (16). Measurement variability contributing to reliability estimates arises from two possible sources: the equipment and experimental procedures, and physiological variability within the population tested. Our use of a motor-driven electronic transducer may have reduced the variability of pressure-pain threshold measurements compared with assessment using a manual transducer. Although manual pressure-pain transducers have been shown to provide reliable estimates of pain threshold in previous studies (22-26), the more consistent rate of pressure application afforded by a motor driven system may still be beneficial. We also provided participants with a button switch to indicate pain threshold rather than use a spoken indication, which removes variability associated with the reaction time of the experimenter. A further difference in our conditioning stimuli is that we chose to use a standard conditioning protocol. For this reason, we recommend use of the cold pressor test in the future evaluation of DNIC pathways. The cold pressor test generates a more focal type of pain compared with the diffuse effects of ischemia, and this may contribute to its more consistent activation of descending inhibitory pathways.

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A large extent of the variability in our measures, particularly that detected between sessions, is likely to arise from physiological variability within the nociceptive system. We attempted to minimize this variability by testing at a similar time of day for both sessions and restricting variables that are known to influence the pain modulationary system. One potential source of intersession variability in our study was the inclusion of female participants. The efficacy of the DNIC system is known to increase during the adulatory phase of the menstrual cycle (30). A possible limitation of our study is that this was not controlled in our female participants. However, given the brief duration of the adulatory phase, it is unlikely to have had a marked effect on our results. The small sample of male participants in our study (n=7) also means that a separate analysis of these data would not be statistically appropriate. Another limitation was that we did not standardize the amount of handgrip exercise during the ischemic arm test, which may have contributed to the reduced reliability of this test. Given that the test still consistently elicited a painful response and the absence of a relationship between conditioning pain and the extent of pain inhibition, it is again unlikely to have a marked influence on our study findings.

Our analysis of the time course of conditioned pain inhibition showed that the effects of conditioning may persist for longer than previously believed. Pressure-pain threshold remained elevated at 10 min following both conditioning stimuli, but had returned to baseline by 15 min. This finding suggests that multiple assessments of the nociceptive system within a session should be separated by a minimum of 15 min to ensure the lasting effects of conditioning have terminated.

CONCLUSION

The function of the DNIC system has been reported on in laboratory settings in both healthy and clinical populations. However, little work has addressed the reliability of its assessment. The present study showed that the assessment of DNIC function in healthy participants using a conditioned pain modulation procedure and a motor-driven electronic pressure transducer was reliable within a session; however, the reliability between sessions varied between our two conditioning stimuli. Although the two stimuli gave rise to a similar level of pain inhibition, the cold pressor test provided a more reliable conditioning stimulus that would be appropriate to use to assess DNIC function over multiple sessions. Further investigations of intrasession reliability of the conditioned pain modulation paradigm should be conducted in clinical populations. We also recommended the adoption of a standardized conditioning protocol to improve the reliability and comparability of future investigations.

REFERENCES
