

Autonomic arousal and experimentally induced pain: A critical review of the literature

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BACKGROUND: Autonomic arousal frequently is assumed to be a component of the pain response, perhaps because physiological mechanisms connecting pain and autonomic reactivity can be easily conceptualized. The evidence clarifying autonomic responses specific to painful stimulation, however, has been rather sporadic and lacks coherence; thus, a summary and critical review is needed in this area.

OBJECTIVES: To summarize and integrate findings from 39 experimental investigations from 1970 to 2012 of pain-induced autonomic arousal in humans.

METHODS: Medline and PsycINFO databases were searched for relevant articles. References from these articles were also considered for review.

RESULTS: Painful stimuli increase respiration rate, induce muscle tension, intensify electrodermal activity and dilate the pupils. Cardiovascular activity also increases, but the pattern displayed in response to pain is complex; peripheral vasoconstriction and sympathetically mediated cardiac responses are most typical. Additionally, autonomic expression of pain shows inconsistent relations with verbal and overt motor responses.

CONCLUSIONS: Autonomic arousal can be legitimately measured and modified as one facet of the pain response. Future research should particularly focus on increasing sample size and broadening the diversity of participants. To improve the ability to compare and contrast findings across studies, as well as to increase the applicability of laboratory findings to naturalistic pain, investigators also must enhance experimental design by increasing uniformity or accounting for differences in methodology. Finally, further work remains to utilize more specific assessments of autonomic response and to assess relationships of autonomic reactivity with other cognitive (eg, attention) and affective (eg, anxiety) variables.

Key Words: *Autonomic arousal; Pain; Physiological arousal*

Theoretically, pain can be understood as a subjective, unpleasant experience with both sensory and emotional components (1). Adaptive and natural, acute pain signals a short-term somatic insult that can be addressed in multiple ways based on context (2,3). Since the middle of the 20th century, laboratory-based investigations of experimentally induced pain have increased in number, but such research also has produced skepticism regarding external validity, generalizability and ability to accurately simulate the private experience of pain (4-9). Studying experimentally induced acute pain, however, offers several advantages: control over the physical properties of the stimulus (eg, magnitude, duration), manipulation of related variables and ability to relate quantifiable levels of manipulated variables to levels of participant responding (6,9). In assessment, pain can be conceptualized pragmatically as a construct that can be measured in multiple response modalities: verbal report, overt motor behaviour and physiological activity (10,11). Of the different types of physiological measurements, activity of the two subdivisions of the autonomic nervous system (ANS) – the sympathetic and the parasympathetic nervous systems – are particularly associated with pain (6,12,13). Increased activity in the sympathetic nervous system leads to increases in sweating (electrodermal activity), respiration rate, heart rate, blood pressure,

L'éveil autonome et la douleur induite de manière artificielle : une analyse bibliographique critique

HISTORIQUE : On présume souvent que l'éveil autonome est un élément de la réponse à la douleur, peut-être parce que des mécanismes physiologiques qui relient la douleur et la réactivité autonome peuvent être plutôt complexes. Les données probantes permettant de clarifier les réponses autonomes propres à la stimulation douloureuse sont toutefois plutôt sporadiques et manquent de cohérence. C'est pourquoi un résumé et une analyse critique s'imposent dans ce domaine.

OBJECTIFS : Résumer et intégrer les résultats de 39 recherches expérimentales menées entre 1970 et 2012 sur l'éveil autonome induit par la douleur chez les humains.

MÉTHODOLOGIE : Les chercheurs ont dépouillé les bases de données Medline et PsycINFO pour trouver des articles pertinents. Ils ont également examiné les références de ces articles en vue de l'analyse.

RÉSULTATS : Les stimuli douloureux accroissent le rythme respiratoire, induisent une tension musculaire, intensifient l'activité électrodermique et dilatent les pupilles. L'activité cardiovasculaire augmente également, mais le schéma présenté en réponse à la douleur est complexe. La vasoconstriction périphérique et les réponses cardiaques à médiation sympathique sont très classiques. De plus, les relations entre l'expression autonome de la douleur et les réponses verbales et motrices évidentes sont inégales.

CONCLUSIONS : L'éveil autonome peut être mesuré et modifié de manière légitime comme une facette de la réponse à la douleur. Les prochaines recherches devraient s'attacher tout particulièrement à accroître la taille de l'échantillon et à élargir la diversité des participants. Pour mieux comparer et contraster les résultats entre les études et pour accroître l'applicabilité des résultats de laboratoire à la douleur naturelle, les chercheurs doivent également améliorer leur méthodologie expérimentale en favorisant l'uniformité ou en tenant compte des différences de méthodologie. Enfin, d'autres travaux devront faire appel à des évaluations plus précises de la réponse autonome et évaluer les relations à la réactivité autonome avec d'autres variables cognitives (p. ex., attention) et affectives (p. ex., anxiété).

vascular vasoconstriction and pupil dilation. Although parasympathetic activation generally results in responses opposite those of the sympathetic nervous system, the two branches can have more complex and ongoing interactions, particularly regarding cardiac activity (12). For example, although parasympathetic influence is typically the dominant cardiac influence and mediates decreased heart rate variability (ie, changes in the interval between heart beats) coupled with increased heart rate, increased heart rate due to diminished cardiac pre-ejection period (ie, the interval between ventricle contractions) is more sympathetically mediated (12,14,15).

Despite recognition of the need to assess pain across modalities (7,8,16), pain remains difficult to measure, particularly from a psychophysiological perspective (17). Perhaps because researchers can readily describe how physiological mechanisms should associate pain with autonomic arousal, investigators have long noted connections between pain and autonomic arousal (6,14,18-20). In an early review of pain and autonomic arousal published several decades ago (6), pain was noted to quicken respiration rate, and increase blood flow to muscles, muscle tension, blood pressure, pulse rate, stroke volume and peripheral vasoconstriction. Difficulties with assessing a stimulus-specific autonomic response to pain were also noted (6), such as individual

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response stereotypy (14) and the law of initial values (21). Similarly, a more recent review of the extant literature for infants and young children by Sweet and McGrath (22) has suggested that pain in this age group increases heart rate, blood pressure and skin conductance, and decreases vagal tone.

PURPOSE AND ORGANIZATION OF ARTICLE

Since the 1960s, technology for autonomic assessment has advanced (14,17). Nevertheless, research in the past several decades dedicated to clarifying the autonomic response to laboratory-induced acute pain – beyond superficial assumptions of a relationship – has been sporadic and lacks coherence.

The purpose of the current review is to promote a clearer understanding of the physiological component of the acute pain response in humans by critically examining empirical studies measuring autonomic response to experimentally induced painful stimulation. In addition to clarifying which autonomic responses are specific to pain, the review also examines the relationships between autonomic responses and responses in other measurement modalities.

To assemble literature, Medline and PsycINFO databases were searched (key words: 'pain', 'autonomic arousal', 'physiological arousal'). References from resultant articles were considered for review as well. The present review included only articles in which autonomic arousal was measured either as a change from baseline or as a form of comparison across groups in response to a laboratory-induced stimulus clearly identified as painful. Thus, the following studies were excluded: studies measuring autonomic arousal as a response to chronic or naturally occurring acute pain; studies that did not explicitly characterize stimulation as painful (eg, not merely stimulating nerve fibers associated with nociceptive reflexes); and studies not clearly measuring autonomic activity at the time of painful stimulation, in response to the stimulation, as a change from baseline or group comparison. Additionally, investigations of arousal affecting pain responding represent a separate line of research. Furthermore, based on literature suggesting general developmental differences between children and adults regarding pain (16), the review primarily focused on studies of adults. Although studies with children were not necessarily excluded, no article included in the review involved participants younger than eight years of age, and studies in the review by Sweet and McGrath (22) were not included. These inclusion and exclusion criteria were used to set a reasonable scope for a single review, to reduce ambiguity in interpretation, and to minimize experimental design differences that may limit comparison and contrast across studies. Finally, although controlled by the somatic nervous system, muscle tension was assessed as a correlate of autonomic arousal in several experiments (23) and was included in the review as a complementary component of the ANS in the peripheral nervous system.

Ultimately, 39 articles, published between 1970 and 2012, were identified for inclusion. Organized according to method of pain induction, the results of studies selected are briefly reviewed below and summarized in Tables 1 to 5. Studies including cold pressor stimulation typically involved immersion of participants' hands or feet into a bath of ice water, while studies examining heat stimulation used hot water for immersion or heat thermodes placed on participants' skin. Investigations of pressure stimulation typically used an algometer (24-26) applied to participants' fingers to produce a slowly building pressure sensation, while research using electrical current often presented stimulation to the extremities or face for durations of seconds or less. Finally, studies relying on other, less common methods of pain induction were grouped separately. Following the brief review, an overall critique of strengths and weaknesses across the literature is presented, along with implications and recommendations for future research.

REVIEW OF THE LITERATURE

Cold-pressor stimulation

Significant increases in electrodermal activity and respiratory rate have been reported in response to cold-pressor stimulation compared

with baseline and guided imagery (27). Skin conductance response to cold-pressor stimulation was also increased by greater levels of trait anxiety and was decreased by the social influence of reassurance from an in-group member confederate (28,29). Electrodermal activity, however, was discordant from cold-pressor tolerance (ie, interval until escape [28,29]), possibly because many participants endured the cold pressor for the maximum time, reducing variability in tolerance (29).

Across the lifespan, cold pressor stimulation increased cardiovascular response when compared with baseline (27,30-33), warm pressor (34) and vicarious experience (35). Additionally, imagery-based distraction (28) and odourant administration (36) diminished vasoconstriction and blood pressure responses to cold pressor while simultaneously increasing pain tolerance and decreasing pain report, although greater sensory input from odourant administration may have increased heart rate. Findings for cardiovascular response were not uniform, however, and nonsignificant or discordant results were reported across measures and studies (27,28,31,33,34,36-39). Inconsistencies in cardiovascular findings may be attributable to imprecise blood pressure and cardiac recordings obscuring the relative contributions of sympathetic and parasympathetic influence.

Pupil dilation increased in the first 30 s after cold pressor administration and decreased in response to a hypnosis intervention, but pupil dilation was not correlated either with cardiovascular responses or verbal report of pain (33,40). Finally, although studies examining muscle tension in response to cold pressor stimuli produced conflicting results, the use of a less intense cold pressor stimulus or the use of pleasant and relaxing imagery (27,28) may explain discrepancies from studies producing significant results (30,31).

Algometer pressure stimulation

Although electrodermal activity, respiration rate and cardiovascular activity (with decreased heart rate variability) all increased with algometer pressure stimulation (23,41,42), only respiration rate, of the three, appeared to characterize a stimulus-specific response (23,43,44). None of these three domains of ANS activity, however, was correlated with pain report within subjects (23). Regarding group differences, skin conductance response fluctuations, but not respiration rate or heart rate, were greater in patients with back pain compared with healthy controls (23); electrodermal activity did not differ for women with and without premenstrual syndrome (41).

Pupil dilation, although not tested directly for a stimulus-specific response, increased with increasing levels of algometer pressure stimulation intensity and correlated with pain report (45,46). Muscle tension also increased in response to algometer pressure and differentiated response to pain from response to slides of homicide victims (4,43); nonsignificant results for muscle tension in a study by Peters and Schmidt (23) may be attributable to analysis of muscle tension data from only the initial portion of the study, compared with the entirety of the experiment.

Electrical stimulation

Increased electrodermal activity, cardiovascular activity (particularly heart rate) and pupil dilation with higher electrical shock intensity was consistent across studies (47-53). Furthermore, the autonomic response to electrical stimulation was modifiable. When participants were able to predict the timing of electrical stimulation, paired with a confederate or model displaying tolerance of shock, and engaged in a music listening task, skin conductance, heart rate reactivity and pupil dilation decreased (47,49,50,52). Additionally, when greater shock intensity was used, electrodermal activity and heart rate matched verbal reports of pain (50-52).

Additionally, one study reviewed examined the influence of shock intensity on an index of arousal created from combining skin conductance, heart rate and pupil dilation into a single variable (54). Although men accepted higher stimulus intensities and had higher arousal levels than women, the two sexes did not differ on reported pain level and accuracy (ie, concordance between pain rating and stimulus intensity), but men were more accurate with increased arousal.

TABLE 1
Sample size, sample sex, autonomic nervous system (ANS) measures, pain stimuli details and main findings of cold pressor studies reviewed

Author(s) (reference), year	n	Female, %	ANS measure(s)	Pain stimulus	Main ANS findings
Yamaguchi et al (35), 1978	40	25	Pulse amplitude, heart rate	Ice bar gripped 5 times for 30 s	Compared with vicarious experience, vasoconstriction and heart rate increased during direct experience of the cold pressor
Feuerstein et al (30), 1982	29	58.6	Digital blood volume pulse, heart rate, muscle tension	Cold pressor at 0°C for 60 s	Vasoconstriction, heart rate and muscle tension increased during cold pressor, especially during the first 30 s
Peckerman et al (32), 1991	18	0	SBP, DBP, heart rate	Cold pressor at 1°C 3 times, endured for 180 s	Blood pressure increased up to 150 s after stimulation; heart rate increased for 30 s, then increased again between 90 s and 150 s
Biederman and Schefft (28), 1994	46	100	Skin conductance level, skin temperature, SBP, DBP, muscle tension	Cold pressor at 0°C twice until tolerance	During the second cold pressor test, the skin conductance level of participants with greater trait anxiety increased, while imagery-based distraction decreased skin temperature and muscle tension
Tassorelli et al (33), 1995	10	50	Heart rate, mean blood pressure, pupil dilation	Cold pressor of 4°C endured for 300 s	Pupils dilated and blood pressure increased 30 s and 120 s, respectively, after cold pressor onset
Tomaka et al (34), 1997	43	NR	Total peripheral resistance, pre-ejection period, heart rate, cardiac output	Cold pressor of 1°C endured for 180 s	Vasoconstriction increased during cold pressor when compared with warm pressor
Zeichner et al (66), 1999	42	NR	Pulse rate	Cold pressor of 0°C–4°C endured for 180 s	Participants with less exposure to family pain modelling displayed increased pulse rate during cold pressor
Zeichner et al (39), 2000	42	57.1	Pulse rate	Cold pressor of 0°C–4°C endured for 120 s	Women had increased pulse rate during cold pressor test
Myers et al (38), 2001	104	48.1	SBP, DBP, heart rate	Cold pressor of 1°C–3°C endured until tolerance	Baseline SBP was correlated with pain tolerance. Males had higher heart rate change scores
James and Hardardottir (31), 2002	72	50	SBP, DBP, heart rate, muscle tension	Cold pressor at 2°C delivered twice until tolerance	SBP, DBP and heart rate increased during cold pressor. Muscle tension increased over the course of the experiment
Flora et al (37), 2003	34	82.4	SBP, DBP, pulse rate	Cold pressor at 5°C delivered until tolerance	Pulse rate decreased for participants enduring the cold pressor during a self-control procedure, but not for participants enduring a warm pressor
Foster et al (27), 2003	100	47.0	Skin conductance activity, respiration rate, skin temperature, SBP, DBP, heart rate, muscle tension	Cold pressor at 13°C for 40 s	Skin conductance, respiration rate, SBP and DBP increased during painful stimulation relative to baseline and guided imagery
Raudenbush et al (36), 2004	158	50	O ₂ saturation, SBP, DBP, heart rate	Cold pressor of 3°C delivered until tolerance	Pleasant odours decreased SBP and DBP and increased O ₂ saturation during cold pressor
Walter et al (40), 2005	22	50	Pupil dilation	Ice spray of –50°C delivered twice for 0.5 s	Maximal pupil dilation and absolute pupil diameter in response to cold pressor were both less during hypnotic state than during nonhypnotic state
Platow et al (29), 2007	54	40.7	Galvanic skin response	Cold pressor of 0°C–2°C delivered twice and endured to tolerance	Skin conductance decreased during the second cold pressor trial for participants receiving reassurance from an in-group member

DBP Diastolic blood pressure; NR Not reported; SBP Systolic blood pressure

Heat stimulation

Although studies investigating heat stimulation examined autonomic activity using only electrodermal and cardiovascular activity, responding in both ANS domains increased with painful heat (55-57). The use of more precise cardiac assessments suggested that increased cardiac response was due to enhanced sympathetic activity and diminished parasympathetic activity, which also appeared to drive decreased heart rate with placebo administration (55,57,58). Additionally, heart rate was responsive to hypnotic instructions to alter pain unpleasantness (59).

Electrodermal and cardiovascular activity diverged, however, in their concordance with other response modalities. Male participants exhibited greater skin conductance levels but reported less pain and arousal, and correlations between skin conductance level and participant report failed to reach statistical significance, perhaps because of insufficient power (55). In contrast, the changes in cardiovascular activity were closely related to report of pain across studies, particularly for males (55,57).

Other stimuli

Three additional studies examined other methods of pain induction. Although heart rate response did not increase with ascorbic acid injection compared with saline injection (60), injection of glutamate into myofascial trigger points produced vasoconstriction comparable with that produced by maximum inspiratory breath hold, which is known to sympathetically increase vasoconstriction (61). Finally, in a study of placebo analgesia, heart-rate response was related to painful stimulation; although there was concordance between pain report and heart-rate response following the administration of saline, atropine and naloxone, propranolol reduced pain reporting but not heart-rate response (62).

CRITIQUE OF THE LITERATURE REVIEWED

Sample issues

The frequent use of college students willing to endure experimentally induced pain places a limit on the scope of generalization of the

TABLE 2
Sample size, sample sex, autonomic nervous system (ANS) measures, pain stimuli details and main findings of algometer pressure pain studies reviewed

Author(s) (reference), year	n	Female, %	ANS measure(s)	Pain stimulus	Main ANS findings
Davidson and Neufeld (43), 1974	60	100	Skin conductance response, respiration rate, heart rate, muscle tension	Algometer pressure for 5 trials at threshold and 5 trials within 0.2 g of tolerance	Increased respiratory rate and increased muscle tension differentiated pain from a psychological stressor
Linden (44), 1985	60	53.33	SBP, DBP, heart rate	Algometer pressure of 400 g delivered for 180 s	Heart rate, SBP and DBP increased less during algometer stimulation when compared with mental arithmetic and projective testing
Kuczmierczyk and Adams (41), 1986	21	100	Skin conductance level, heart rate	Algometer pressure of 2000 g endured twice until tolerance	Skin conductance level and heart rate increased at pain threshold across menstrual cycle phases
Peters and Schmidt (23), 1991	40	0	Skin conductance level and response, respiration rate, heart rate, muscle tension	Algometer pressure of 1700 g, delivered 6 times, endured for 70% of tolerance time	Skin conductance response fluctuations, respiration rate and heart rate increased with pressure stimulation, while heart rate variability decreased
Ellermeier and Westphal (45), 1995	16	50	Pupil dilation	Algometer pressure of 750 kPa, 940 kPa, 1190 kPa and 1500 kPa delivered four times each for 20 s	Pupil dilation increased with increased pressure intensity
Carter et al (4), 2002	80	50	Heart rate, muscle tension	Algometer pressure, delivered twice, until tolerance	Heart rate decreased from the first algometer trial to the second. Trapezius muscle tension increased during algometer stimulation.
Höfle et al (46), 2008	20	100	Pupil dilation	Algometer pressure of 800 g and 950 g, delivered six times each for 20 s	Pupil dilation was greater 10 s to 20 s after the onset of the 950 g stimulus than the 800 g stimulus
Kyle et al (42), 2009	96	50	Heart rate	Algometer pressure of 1000 g delivered twice and 2000 g delivered once until tolerance	Heart rate was higher during the 2000 g stimulus, compared with the 1000 g stimulus, but only when the 2000 g was delivered first

DBP Diastolic blood pressure; SBP Systolic blood pressure

TABLE 3
Sample size, sample sex, autonomic nervous system (ANS) measures, pain stimuli details and main findings of electrical stimulation studies reviewed

Author(s) (reference), year	n	Female, %	ANS measure(s)	Pain stimulus	Main ANS findings
Lykken et al (52), 1972	48	0	Skin conductance level, heart rate	Electric current, 0.5 s in duration, delivered 48 times at tolerance	Skin conductance and heart rate were lower when participants could predict the timing, but not location, of electrical stimulation
Craig and Neidermayer (49), 1974	40	0	Skin conductance level, heart rate	Electric current, 0.5 s in duration, increasing in intensity to threshold	Skin conductance level and heart rate increased across groups with electrical stimulation
Lanzetta et al (51), 1976	20	50	Skin conductance response	Electric current, 2 s in duration, delivered 41 times at intensities of 33%, 66% and 99% of tolerance	Electrodermal response increased with increased electrical stimulation intensity
Craig and Prkachin (50), 1978	20	100	Skin conductance response, skin potential response, heart rate	Electric current, 0.5 s in duration, increasing in intensity to threshold, followed by 12 presentations each of 2 mA, 3 mA, 4 mA, 5 mA and 6 mA	Skin conductance response increased during stimulation. Heart rate increased after electrical shock, particularly with elevated shock intensity
Chapman et al (48), 1999	20	45	Pupil dilation	Electric current, 5 ms in duration, at four individualized intensities, given in 2 blocks of 64	Pupil dilation increased as stimulus magnitude increased. Peak pupil dilation occurred later with increasing stimulus intensity
Chapman et al (54), 2002	100	44	Pupil dilation, skin conductance response, heart rate	Electric current, 5 ms in duration, at three individualized intensities, given in 4 blocks of 36	Increased stimulus intensity led to increased attention to stimulus, which led to increased ANS arousal
Vassend and Knardahl (53), 2005	58	100	Skin blood flow, mean arterial pressure, heart rate	Electric current, delivered 5 times, increasing in intensity up to tolerance	Heart rate, mean arterial pressure, facial vasodilation and digital finger vasoconstriction increased during stimulation
Bradshaw et al (47), 2012	49	39.6	Pupil dilation	Electric current, 5 ms in duration, delivered in 9 blocks of 24, at 20%, 50% and 80% of individual tolerance	Pupil dilation increased with increasing stimulus intensity but decreased with increasing complexity of a music listening task

39 studies reviewed (63). Only seven studies did not rely on participants from a traditional college student age range (23,27,30,41,50,53,62). Overutilization of college-age students is especially problematic

because many pain responses differ across the lifespan; for example, nervous system activity latency increases and amplitude decreases in older adults (16). How such differences impact autonomic response to

TABLE 4
Sample size, sample sex, autonomic nervous system (ANS) measures, pain stimuli details and main findings of heat stimulus studies reviewed

Author(s), year (reference)	n	Female, %	ANS measure(s)	Pain stimulus	Main ANS findings
Möltner et al (56), 1990	12	50	Respiration rate, heart rate	Heat thermode delivered 2 times at 40°C, 2 times at 42°C, 2 times at 44°C and 14 times within $\pm 1.5^\circ\text{C}$ of pain threshold	Heat stimulation evoked monophasic and biphasic increase in heart rate, and greater stimulus intensity was associated with greater mean heart rate increase
Rainville et al (59), 1999	Exp 1: 17 Exp 2: 20	29.41 35	Heart rate	Hot pressor of 46.5°C delivered 15 times for 60 s or up to tolerance Hot pressor of individualized intensity delivered 8 times for 60 s	Hypnosis instructions to decrease pain unpleasantness decreased prestimulus resting heart rate Hypnosis instructions to decrease pain unpleasantness decreased heart rate
Tousignant-Laflamme et al (57), 2005	39	51.28	Skin conductance level, heart rate	Hot water at 47°C for 120 s	Skin conductance level and heart rate increased during heat stimulation
Aslaksen et al (55), 2007	64	50	Skin conductance level, heart rate	Heat thermode at 48°C 15 times for 12 s	Skin conductance level and heart rate increased with stimulation
Aslaksen and Flaten (58), 2008	63	51	Heart rate	Heat thermode at 46°C 10 times for 240 s	Placebo administration, relative to no placebo, decreased heart rate

Exp Experiment

TABLE 5
Sample size, sample sex, autonomic nervous system (ANS) measures, pain stimuli details and main findings of other stimulus studies reviewed

Author(s), year (reference)	n	Female, %	ANS measure(s)	Pain stimulus	Main ANS findings
Pollo et al (62), 2003	Exp 1: 37 Exp 2: 58	81.1 53.5	Heart rate	Electric current, delivered 4 times at 1.5 times individual pain threshold Tonic, ischemic arm pain induced via tourniquet procedure	Placebo injection decreased heart rate during electrical stimulation, relative to no placebo injection Placebo administration of saline and atropine produced a decrease in heart rate. Naloxone and propranolol did not decrease heart rate
Porro et al (60), 2003	56	57.1	Heart rate	Injection of ascorbic acid	There were no differences in heart rate for injection of ascorbic acid versus injection of saline or touching the foot with a needle
Kimura et al (61), 2009	14	35.7	Skin blood flow, skin temperature	Injection of 0.1 mL glutamate into latent myofascial trigger points	Injection of glutamate decreased skin blood flow and temperature. Vasoconstriction was similar to maximum inspiratory breath hold

Exp Experiment

experimentally induced painful stimulation across the lifespan remains uninvestigated.

Biological sex also emerged as a sampling issue. Ten studies recruited participants exclusively of one sex. Of the 29 studies involving participants of both sexes, only seven reported statistically significant differences according to sex in ANS pain response: males displayed increased cardiovascular reactivity and greater pain threshold and tolerance, responses that are more closely associated with report of pain than for females (4,27,38,39,54,55,57). Previous research (64,65), however, has suggested a minimum of 82 participants is needed for sufficient statistical power (0.70) to detect sex differences in response to experimentally induced pain, and only five studies reviewed collected samples of this size or larger (27,36,38,42,54). As such, the studies reviewed offered minimal opportunity to properly assess sex differences or similarities with adequate statistical power.

Addressing racial, ethnic and cultural similarities and differences also proved to be a significant weakness for many studies reviewed. Only five studies reviewed even reported the percentage of participants in different racial or ethnic categories (4,27,32,38,42).

Procedure and design issues

Procedure issues: Studies using electric current typically presented shocks lasting seconds or less in duration, with ANS response often measured after stimulus offset. In contrast, cold pressor or pressure stimulation often occurred over the course of several minutes, and

autonomic response was recorded during stimulation. The timing of pain during cold pressor (within 1 min) and algometer (slowly building) stimuli differ as well (6,24,25). Although such differences in duration and peak of noxious stimulation, as well as timing of autonomic assessment, make it more difficult to abstract generalizations or explain conflicting results for cardiovascular responding and muscle tension, patterns of responding that occurred similarly across different types of noxious stimuli for electrodermal activity, respiration and pupil dilation appear to be more robust.

Another issue limiting generalization across studies is the difference between individualized and uniform pain stimuli. Noxious stimulation alone does not necessarily equate with painful stimulation or produce pain responding, and investigators must balance attempts at uniformity in stimulation with individual differences in pain report, threshold and tolerance. Twelve studies reviewed changed the pain stimulus for each individual, which may reduce external validity and generalization to more natural contexts, as well as introduce bias from variation in accuracy of pain reporting (23,43,47-52,54,56,59,62). Experiments with uniform stimuli that allowed participants to escape the noxious stimulus when they reached pain tolerance, however, created a confound of different stimulus durations (4,28,29,31,36-38,41,42,53,59), and when the same stimulus was presented for the same duration, the stimulus was often of relatively reduced intensity or duration (27,35,40,44-46,55). When studies used truly uniform and

painful stimuli, they generally found significant results for autonomic response (30,32-34,39,57,58,61,62,66).

Despite the potential influence of anxiety or fear of upcoming noxious stimulation, or the influence of being in a novel laboratory environment, only four studies reported waiting for stable autonomic activity before painful stimulation began (27,31,38,61), with seven other studies including prestimulation adaptation periods lasting 10 min or longer (33,35,41,44,45,49,51). Similarly, studies administering stimulation more than once differed from seconds to days in their interstimulus intervals. These vast differences in pre- and interstimulus adaptation periods impede interpretation across studies because the law of initial values suggests these levels influence later levels of arousal (21,67).

A final noteworthy procedural limitation across studies involves the orienting and defensive responses. Disagreement exists regarding how best to conceptualize these responses because of equivocal results across investigations (68-70), providing an opportunity for investigations of autonomic response to laboratory-induced pain to contribute to this literature. Briefly, the orienting response enhances attention and sensitivity to moderate novel stimulation and involves cephalic vasodilation, peripheral vasodilation, increased electrodermal activity and decreased heart rate; in contrast, the defensive response facilitates protection from more intense or threatening stimulation and includes both cephalic and digital vasoconstriction, a greater increase in electrodermal activity and increased heart rate (67,68,70-73). The studies reviewed largely missed the chance to facilitate understanding of these constructs, which also may help to explain contradictory or unexpected findings. For example, if the use of a less intense stimulus in some studies elicited an orienting response, the deceleration of heart rate would be the opposite of the expected reaction. Additionally, as the cardiac component of the defensive response may occur over 80 s, with two sequences of heart rate acceleration followed by deceleration, the tendency of many studies to average heart rate over time may have obscured these changes (70).

Design issues: The majority of the studies reviewed failed to distinguish stimulus-specific response patterns by examining painful stimuli alone. Although eight studies did make comparisons with other stimuli, only some comparative stimuli were informative: slides of homicide victims (43), arithmetic and projective test stressors (44), warm pressor (34,37), maximum inspiratory breath hold (61) and vicarious experience (35).

Compared with a relative lack of assessment of stimulus-specific responses, most investigations assessed moderators and mediators of autonomic response to noxious stimulation. Quasiexperimental moderating variables included premenstrual syndrome (41), chronic low back pain (23), trait anxiety (28,31) and exposure to familial pain modelling (66); similarly, experimental manipulation of social influence (29,49,50), hypnosis (40), experimenter sex (4,55), stimulus intensity sequence (42), stimulus predictability (52), imagery-based distraction (28), music engagement (47), nonverbal expression of pain (51), placebo administration (58,62) and scent (36) generally impacted autonomic activity. Finally, studies of mediation provided evidence that autonomic response increases with increased stimulus intensity (42,56), increased report of pain unpleasantness (57,59) and increased attention to the pain stimulus (54).

Measurement and assessment issues

Given that autonomic response was not always uniform within a single investigation, research measuring only one domain could have missed important findings, and comparisons across studies focusing exclusively on different domains may not be valid. However, 16 studies examined cardiovascular response only, five studies examined pupil dilation only and two studies examined electrodermal activity only. Similarly, most studies assessing cardiac response focused on heart rate, offering little insight into sympathetic versus parasympathetic mediation. The six studies reviewed that included more in-depth cardiac measures indicated both a parasympathetic and a sympathetic influence on cardiac response to pain, although the sympathetic influence

predominated (23,34,55,57,58,62). Thus, even if response in a single ANS domain tends to be a more accurate indicator of pain, it may not be sufficient to measure autonomic activity in that domain alone.

The duration of autonomic response measurement also presented a problem for many studies reviewed. Investigations assessing responses for brief, selected durations may have missed patterns of responding occurring outside of measurement periods such as differences in autonomic responding reported in investigations that included poststimulation assessment (4,23,28,30,33,42,56,62). In grouping autonomic responses measured continuously for extended periods into average values without accounting for habituation (35,43,51,52), however, studies could have missed important patterns of responding because other studies offered evidence that habituation occurred in response to repeated stimulation (23,47,50,53,55).

Finally, studies varied in the other modalities of pain responding recorded and analyzed, with the overt motor response of escape assessed in only nine studies (4,28,29,31,36,38,41,42,53). Furthermore, statistical comparisons were made between autonomic and other responses in only 12 studies (23,33,38,43,45,46,52,54,56-59); other investigators simply observed similarities or differences in response patterns. Increased autonomic response was generally related to increased report of pain, but without a priori clarity of theory and hypothesis, post hoc interpretation of results often failed to consider multiple potential relations among modalities. For example, some investigators may interpret increased arousal coupled with increased tolerance as signalling greater acceptance of physiological sensations, but other researchers may anticipate that decreased arousal should accompany lengthened tolerance because they hypothesize that arousal mediates tolerance.

Statistical issues

Smaller samples can be appropriate when studying a larger effect, but the studies reviewed with smaller sample sizes offered no justification for sample size, which reduces power and impairs interpretation of nonsignificant results. Only six studies reviewed (4,27,36,38,42,54) included a sample of ≥ 74 participants, and seven studies had groups with as few as 10 participants (30,33,35,41,49,50,59). Furthermore, many researchers presented nonsignificant findings as evidence of no effect, which is faulty logic in a null hypothesis testing paradigm, and only six studies reviewed reported statistics regarding effect size to offer insight into the clinical or practical utility of findings (27,29,42,47,48,54).

Finally, many experiments reviewed included a poor selection of analyses of their data. Only seven studies with repeated measures utilized analyses that addressed sphericity (23,32,46-48,53,60), the frequently violated assumption that correlations between all values of a within-subjects variable will be similar (74-76). Additionally, most investigations inadequately controlled for baseline levels of arousal by analyzing change scores; four studies (4,28,29,44) more properly used analysis of covariance or residualized change scores (12). Discriminant function analysis (43) and causal or mixed-effects modelling (47,48,54), however, offered innovative approaches to analysis.

INTEGRATION OF STUDIES REVIEWED AND CONCLUSIONS

State of the literature

The present review is the first formal summary and critique of research investigating autonomic expression of experimentally induced pain in more than 40 years (6). Respiration rate, pupil dilation and electrodermal activity consistently increased during painful stimulation across studies, as well as muscle tension when stimuli were more intense and delivered for a uniform length of time. Cardiovascular responses were more heterogeneous among studies, with neither heart rate nor blood pressure demonstrating consistent responding. Greater precision in measurement revealed more consistent cardiovascular increases in sympathetic activity, with peripheral vasoconstriction and sympathetically driven cardiac responses (eg, heart rate

variability), although decreased parasympathetic activity did play a role in cardiac responding, consistent with increased respiration rate (12). Additionally, the autonomic component of pain expression was influenced in the expected direction by several variables, including imagery (28), social influence (29), hypnosis (40), engagement with a music listening task (47), attention (54), predictability (52), anxiety (28) and unpleasantness (57,59).

Perhaps most noteworthy regarding the reviewed literature are the numerous barriers to drawing more confident and thorough conclusions; relative to technological innovations, increases in knowledge have not kept pace. Small sample sizes and minimal reporting of effect size cloud interpretation of nonsignificant findings. Studies differed greatly in precision and timing of autonomic assessment, as well as in the individualization or uniformity of stimuli. Many studies failed to address the confounding overlap between painful stimuli and stressful stimuli, which may be expected to elicit similar responding, to illuminate a stimulus-specific ANS pain response. Tentative conclusions suggest decreased skin temperature and increased respiration rate, muscle tension and vasoconstriction may especially characterize autonomic expression of pain (34,43,61). Additionally, although autonomic response typically was related to verbal report, few studies informatively investigated other concordance across response modalities. Considering the disadvantages of the literature, however, the broad conclusions that can be drawn may be quite robust; they also provide a foundation for future research that addresses these limitations.

Conceptual and clinical implications

The literature regarding pain-induced autonomic arousal has several ramifications. First, painful stimulation produces general autonomic arousal that rises with increasing levels of stimulus intensity, suggesting that autonomic arousal can be assessed as one indicator of pain in research and clinical settings. Not all autonomic responses, however, are equal in relation to pain. Electrodermal or pupillary measures could detect non-pain-specific arousal, and imprecise cardiovascular measures may not be evidence of a pain response. Respiration rate, muscle tension, heart rate variability and peripheral vasoconstriction are more likely to provide a clearer indication of the influence of a painful stimulus.

Second, pain-induced arousal is not simply static; rather, autonomic expression of pain can be modified. Pain management strategies can reduce arousal to decrease the impact of pain on behaviour. Given the importance of respiration, heart rate variability and muscle tension, diaphragmatic breathing or progressive muscle relaxation may be especially effective; however, this assumption requires more direct investigation. Such research has found slowed breathing reduces report of pain (77).

Third, pain remains a construct that must be assessed multimodally. Any conclusions drawn from studies reviewed should not be viewed as support for elevating the veridical status of autonomic responses above verbal report or overt motor behaviour. Collecting measurements from all modalities remains important for assessing all facets of pain sufficiently and comprehensively.

Future directions

Much work remains to improve understanding of the autonomic response to painful stimulation. First, investigators must use better comparative stimuli to clarify a stimulus-specific autonomic response to painful stimulation. For example, investigations from before the time period covered by the present review compared direct experience of painful stimulation to vicarious, or observational, stimulation, suggesting heart rate accelerates with painful stimulation and decelerates with observation of others receiving painful stimulation (78-80). Similar comparisons are needed in the current literature.

Second, the current literature tends to rely excessively on verbal report; autonomic and other psychophysiological methods (and overt behavioural measures as well) are used much too infrequently. Not only must assessment of pain responding be multimodal, but statistical comparisons must be made among modalities to better elucidate

concordance and discordance, rather than simply noting similarities in patterns. Researchers also need to be more specific in the theory organizing their expectation of relations among modalities.

Additionally, differences in methodology across studies, both in administration of painful stimulation and in measurement of autonomic responding, should be better acknowledged and controlled. When possible, it would be ideal to administer stimuli of uniform intensity and duration that are painful to all participants, to balance both internal and external validity, as well as to minimize confounds from differences in participant accuracy, or stimulus duration and intensity. Measures that specifically assess sympathetic and parasympathetic responses will further elucidate the roles of the two branches. Arousal measured over time should be analyzed for trends of shorter duration, as well as patterns of habituation, and more sophisticated statistical analyses should be used to control for individual differences in baseline arousal. Also, to increase power and to help determine if the results found in the studies reviewed apply to other groups, improvements are needed in sample size and demographics; effect sizes must be reported as well.

As a matter of relevance, researchers need to build a stronger case for the relation of experimentally induced pain to acute clinical pain that is either procedural (eg, root canal therapy, tooth extraction) or pathological (eg, kidney stones [nephrolithiasis], arthritis). Better understanding of the relations of autonomic responses to laboratory and naturalistic pain will help illustrate universality of some behavioural principles while revealing factors differentiating contexts.

Because many of the studies reviewed did little to assess or control for cognitive and affective variables frequently associated with pain, these constructs warrant more attention in future research. A significant portion of the pain literature has examined the interaction of fear and anxiety with pain (81,82). That few investigations reviewed included fear or anxiety in their design is especially concerning because these constructs include autonomic arousal as a central feature (11). Also of concern is work to date that blurs the line between fear and anxiety, and pain (eg, using electrical shock to induce fear and the threat of shock to induce anxiety [83]). Similarly, attention is one mechanism through which pain may influence behaviour (84-86); however, the extent to which attention influences the autonomic component of the pain response has been underinvestigated.

To conclude, the literature supports an increase in autonomic response as a component of acute pain, with variations in the response based on the domain of ANS activity measured. Limitations and flaws in the extant literature, however, prevent drawing firm conclusions about a specific ANS response to pain. Tentatively, it may be suggested that electrodermal activity increases and the pupils dilate in response to pain, but respiration rate, muscle tension, heart rate variability and peripheral vasoconstriction are more likely to characterize a unique, signature autonomic response to experimentally induced pain. Future research will offer clarification of the specific nature of this response and how it contributes to researchers' conceptualization of the construct of pain. Perhaps most importantly, concordance between autonomic activity and other response dimensions should not be assumed. Measures in multiple modalities should be included to most sufficiently measure the pain response, to further increase understanding of how autonomic activity fits into the larger picture of laboratory-induced acute pain. Indeed, measurement of autonomic activity is, and should be, a vital element of pain research.

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