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Anger Management Style and Endogenous Opioid Function: Is Gender a Moderator?

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Abstract This study explored possible gender moderation of previously reported associations between elevated trait anger-out and reduced endogenous opioid analgesia. One hundred forty-five healthy participants underwent acute electrocutaneous pain stimulation after placebo and oral opioid blockade in separate sessions. Blockade effects were derived reflecting changes in pain responses induced by opioid blockade. Hierarchical regressions revealed that elevated anger-out was associated with smaller pain threshold blockade effects (less opioid analgesia) in females, with opposite findings in males (interaction $p < .001$). Similar marginally significant interactions were noted for blockade effects derived for nociceptive flexion reflex threshold, pain tolerance, and pain ratings ($p < .10$). Anger-in was also associated negatively with pain threshold blockade effects in females but not males (interaction $p < .05$). Across genders, elevated anger-in was related to smaller pain tolerance blockade effects ($p < .01$). Overlap with negative affect did not account for these opioid effects. The anger-in/opioid association was partially due to overlap with anger-out, but the converse was not true. These findings provide additional evidence of an association between trait anger-out and endogenous opioid analgesia, but further suggest that gender may moderate these effects. In contrast to past work, anger-in was related to reduced opioid analgesia, although overlap with anger-out may contribute to this finding.

Keywords Anger-in · Anger-out · Anger management style · Opioids · Pain · Gender

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Introduction

Previous research has demonstrated that the manner in which anger is regulated influences responses to acute and chronic pain (e.g., Burns et al. 2003; 2004; Lombardo et al. 2005; Keefe et al. 2001; Kerns et al. 1994). Two anger management styles have been the primary focus of this research: anger-in (managing anger through inhibition of expression) and anger-out (managing anger via direct physical or verbal expression). A recent review concluded that elevated trait anger-out is frequently associated with either increased acute pain responsiveness or greater levels of chronic pain intensity and dysfunction, although non-significant findings have been reported (Bruehl et al. 2006). Elevated trait anger-in has also demonstrated associations with increased pain responsiveness in several studies (Bruehl et al. 2002; Burns et al. 2004; Gelkopf 1997; Kerns et al. 1994).

Mechanisms underlying the pain-related effects of anger management styles are not well-understood. However, some evidence suggests that endogenous opioid system dysfunction may contribute to the pain-related effects of trait anger-out (Bruehl et al. 2002; 2003b). Specifically,

individuals low in trait anger-out reported greater acute pain intensity following opioid blockade than when under placebo, whereas those high in anger-out did not, suggesting absence of endogenous opioid analgesia in the latter group (Bruehl et al. 2002). In addition, opioid blockade responses suggested that opioid dysfunction partially mediates the positive relationship often reported between anger-out and chronic pain intensity (Bruehl et al. 2003b). These findings suggest that greater acute and chronic pain responsiveness associated with trait anger-out may be due in part to impaired ability to elicit endogenous opioid analgesia. Recent research using an alternative index of endogenous opioid function has provided further direct support for this opioid dysfunction hypothesis. Individuals higher in anger-out displayed less release of plasma beta-endorphin (an endogenous opioid with significant analgesic properties) in response to pain than did those lower in anger-out (Bruehl et al. in press). Findings that individuals higher in anger-out also exhibit reduced cortisol response to opioid blockade further suggest altered opioid function in this group (al'Absi and Bongard 2006). Finally, indirect support for the opioid dysfunction hypothesis is provided by findings that the hyperalgesic effects of trait anger-out on chronic pain intensity are eliminated by use of exogenous opioid medications, as might be expected if exogenous opioids were in effect substituting for deficient endogenous opioids (Burns and Bruehl 2005). Taken together, the findings above provide at least preliminary support for the hypothesis that the pain-related effects of trait anger-out are mediated in part by an association with endogenous opioid dysfunction.

Although anger-in, like anger-out, has also been found to be associated positively with acute and chronic pain intensity in several studies (Bruehl et al. 2002; Burns et al. 2004; Gelkopf 1997; Kerns et al. 1994), research to date does not suggest that opioids are involved in these effects. Anger-in was not associated significantly with the effects of opioid blockade on acute pain responses (Bruehl et al. 2002), nor with the magnitude of beta-endorphin release in response to acute pain (Bruehl et al. in press). At least one prior study suggests that the hyperalgesic effects of anger-in may be due in part to shared variance with general negative affect (Bruehl et al. 2003a).

Factors which may moderate the opioid/anger-out links described above have not been systematically explored. Limited prior work suggests that gender may influence the relationship between anger management style and pain responses (Burns et al. 1996, 1998). For example, high levels of anger-out were associated with low levels of improvement in lifting capacity among male but not female chronic pain patients undergoing multidisciplinary pain treatment (Burns et al. 1998). Moreover, high anger-out in combination with elevated hostility predicted elevated pain severity among female chronic pain patients, although the opposite was found in male patients (Burns et al. 1996). The presence and nature of any gender interactions affecting associations between opioid function and anger-out have not been explored previously. This is due in part to the relatively small sample sizes available for testing such interaction effects and unequal gender distributions in previously reported samples (Bruehl et al. 2002, 2003b; in press). An existing dataset using an opioid blockade methodology in a large sample with relatively even gender distribution (from France et al. 2005) provided an opportunity to both replicate previous findings of an association between anger-out and opioid dysfunction, and to test systematically for gender interactions that may influence these associations. The present study had three aims: (1) determine whether higher scores on anger management style measures (anger-in, anger-out) were associated with smaller effects of opioid blockade on acute pain responses as would be expected if they were associated with opioid dysfunction, (2) explore any moderating effects of gender on these relationships, and (3) determine the extent to which any such observed associations are due to shared variance with general negative affect rather than unique effects of anger management styles.

Methods

Design

A mixed between (anger-in and anger-out) and within (placebo/opioid blockade) subjects design was used.

Participants

The sample reflected participants from a previously published study (France et al. 2005), and included those who had completed the anger management style measure that was the focus of the current study and who had data sufficient to calculate at least one blockade effect outcome measure (see below). The final sample consisted of 145 healthy young adults who were recruited from Ohio University (Athens, Ohio) and the University of Minnesota (Duluth, Minnesota). Of the study participants, 53.1% were male and 77.9% were of white non-Hispanic race/ethnicity, with an overall mean age of 19.2 ± .12 years. Psychological and pain outcome variables are summarized by gender in Table 1. Males and females had comparable levels of trait anger-in and anger-out, although females reported significantly more symptoms of depression and higher trait anxiety. Females exhibited significantly lower pain threshold and tolerance, and higher pain ratings, although

Table 1 Mean (±SE) for psychological and pain outcome variables by gender

Variable	Gender	
	Male (n = 77)	Female (n = 68)
Anger-in	16.0 ± .36	15.5 ± .49
Anger-out	15.2 ± .39	15.2 ± .45
Depression	9.62 ± .69*	13.0 ± 1.11
Trait anxiety	32.4 ± .70*	35.6 ± 1.13
PRI—Placebo	6.5 ± .54	8.0 ± .73
PRI—Naltrexone	6.3 ± .55*	9.4 ± .79
Pain threshold (mA)—Placebo	19.4 ± 1.03	17.2 ± 1.13
Pain threshold (mA)—Naltrexone	22.1 ± 1.11*	17.1 ± 1.19
Pain tolerance (mA)—Placebo	33.6 ± .95*	26.4 ± 1.11
Pain tolerance (mA)—Naltrexone	34.5 ± .94*	28.2 ± 1.15
NFR threshold (mA)—Placebo	14.5 ± .91	12.7 ± 1.19
NFR threshold (mA)—Naltrexone	15.4 ± 1.14	14.8 ± 1.25

* $p < .05$

Note: PRI = McGill Pain Questionnaire Total Pain Rating Index Score

these effects were generally restricted to the naltrexone condition. All participants received compensation of $20 per hour of testing.

Initial Screening

An initial screening questionnaire was used to identify healthy individuals with no history of major medical problems or routine use of medication (other than birth control). Those who met these inclusion criteria, expressed an interest in participating, and completed an informed consent were then scheduled for a brief medical screening to confirm the absence of any medical contraindications to testing. Participants were next scheduled for two 3-h laboratory sessions, which were scheduled on average 5 ± .7 days apart to allow for clearance of naltrexone. To control for potential menstrual cycle phase effects, women were tested within 2–7 days after the onset of menses. All participants were asked to refrain from caffeine, nicotine (11% of the sample smoked), alcohol, and strenuous exercise for at least four hours before their arrival at the laboratory, and from analgesic medication for 24 h prior to testing.

Procedure

The experimental procedure was administered by a female experimenter at each testing site. To start each testing session, participants completed a brief questionnaire to assess compliance with the requested dietary, exercise, and medication restrictions. In addition, women took a One-Step E.P.T.™ pregnancy test to confirm that they were not pregnant. Once participants were cleared to continue, they completed a 10-min resting baseline of blood pressure and heart rate readings. They then consumed a gel capsule that contained either a 50 mg dose of naltrexone (a nonselective opioid receptor antagonist) or placebo, with drug order randomly assigned and administration double-blinded. A 50 mg dose of naltrexone was chosen because it is a standard clinical dose used in treatment of individuals with opiate and alcohol dependence, and produces extended opioid receptor blockade (up to 24 h). Participants then sat quietly for one hour (average time to peak drug effects) to allow time for drug absorption. During this interval they completed a number of questionnaires, read quietly, and then had stimulating and recording electrodes attached according to the procedures described below. Questionnaires completed included the Center for Epidemiological Studies—Depression Scale (Radloff 1977), the trait form of the State-Trait Anxiety Inventory (Spielberger et al. 1970), and the Anger Expression Inventory (Spielberger et al. 1985). The last measure includes separate subscales assessing anger-in (managing anger via inhibition of expression) and anger-out (managing anger through direct verbal or physical expression). This anger-out scale has demonstrated previous associations with measures of opioid function (Bruehl et al. 2002, 2003b, in press).

Following the absorption period, a second 10-min baseline of blood pressure and heart rate was obtained. Three nociceptive flexion reflex (NFR) assessments were then conducted, followed by electrocutaneous pain threshold and tolerance assessments as described below.

Electrode Attachment

To prepare participants for stimulating and recording electrode application, the skin at the electrode sites was cleaned with alcohol and then abraded with Omni Prep electrode paste. An electrode impedance of less than 10 kOhm, verified using a UFI Checktrode (model MKII), was achieved before proceeding. To permit NFR assessment, electromyographic (EMG) activity was recorded from the biceps femoris muscle of the left leg using a DelSys, Bagnoli-2 differential amplifier. The active electrode was placed over the left biceps femoris muscle 10 cm superior to the popliteal fossa, and a reference electrode attached over the lateral epicondyle of the femur. EMG was recorded and processed using a CED Micro1401 analog-to-digital converter and Spike2 software. A Nicolet bar electrode (anode inferior) was attached to the left leg over the retromalleolar pathway of the sural nerve and electrical stimulation was delivered using a Digitimer, DS7A constant-current stimulator.

Electrocutaneous Pain Threshold and Tolerance

Participants were seated in a Hi-Seat rehabilitation chair (model 2000) with a leg rest adjusted to maintain knee flexion at approximately 60 degrees from horizontal. First, NFR threshold was assessed three times, with each assessment lasting approximately 5 min and followed by a 5 min rest period (see France et al. 2005 for details). Upon completion of the NFR threshold assessments, electrocutaneous pain threshold and tolerance levels were measured. Specifically, sural nerve stimulation trials were delivered as a volley of five 1 ms rectangular pulses with a 3 ms interpulse interval (total duration = 17 ms). Stimulation intensity began at 0 mA and increased in 2 mA steps until a maximum stimulation intensity of 40 mA was reached or the participant reached their tolerance threshold. Following each trial, participants rated the perceived stimulation intensity using a verbal rating scale (VRS) with anchors of 0, (no sensation), 1 (sensory threshold), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable).

Pain threshold (in mA) was defined as the first stimulation intensity that received a rating of 50 or greater. Pain tolerance (in mA) was defined as the maximum stimulation intensity that a participant was willing to receive or rated as a 100. Finally, an overall rating of the electrocutaneous stimulation received was provided by the total score on the Pain Rating Index of the McGill Pain Questionnaire—Short Form (Melzack 1987).

Data Reduction

The present study focused on three pain measures obtained during the electrocutaneous threshold and tolerance assessments, including (1) electrocutaneous pain threshold (in mA), (2) electrocutaneous pain tolerance (in mA), and (3) McGill Pain Questionnaire (total Pain Rating Index) scores for the electrocutaneous pain tolerance assessment. Although NFR threshold values were also measured, we restricted our analyses to the first NFR assessment because the second and third assessments were obtained during and immediately after an attentional manipulation (i.e., video game) designed to alter observed threshold levels (see France et al. 2005 for additional details).

As an index of the degree of opioid analgesia elicited by the acute pain stimulation, blockade effects were derived by subtracting placebo condition pain ratings from naltrexone condition pain ratings, and by subtracting naltrexone NFR threshold and electrocutaneous pain threshold and tolerance values from comparable placebo condition values. Thus, positive values for the resulting blockade effects indicate that naltrexone heightened pain responsiveness (increased pain ratings or decreased pain threshold or tolerance). These blockade effects were used as the dependent measures in the analyses described below testing the primary hypotheses.

Statistical Analysis

All analyses were conducted using the SPSS for Windows Version 13 statistical package (SPSS, Inc., Chicago, IL). Preliminary analyses used Pearson correlation coefficients and *t*-tests for group mean comparisons. Preliminary analyses indicated that blockade effects were significantly larger in those who received naltrexone in the first study session ($p < .05$), although drug order was not associated significantly with either anger-in or anger-out ($p > .10$). Possible two- and three-way interactions between the primary variables of interest (gender, anger management styles) and drug order were also tested in preliminary analyses, but were not significant ($p > .10$) with the exception of a significant order × gender interaction ($p < .01$) in analyses of anger-in influences on pain threshold blockade effects. Inclusion of the order × gender interaction in the relevant analysis below did not alter the pattern of effects reported. Therefore, all primary analyses reported below included control for main effects of drug order only.

Primary analyses were conducted to examine the main and interactive effects of anger management style (anger-out or anger-in) and gender on opioid blockade effects derived for acute pain responses. These analyses consisted of hierarchical multiple regressions. Gender was dummy coded (male = 0; female = 1), and interaction terms were computed by multiplying gender by anger-out or anger-in scores, as appropriate. Using anger-out to illustrate, drug order was entered as a control variable in step one, the main effect terms (gender, anger-out scores) were entered in the second step, and the interaction term (anger-out × gender) was entered in the third step. Regressions were conducted separately for each opioid blockade effect variable. The source of significant gender interactions was clarified by calculating simple slopes separately for males and females (Aiken and West 1991). To depict significant gender interaction graphically, the regression equations computed for males and females were solved for hypothetical low and high anger management style values (–1 SD and +1 SD from the mean score of the anger-out or anger-in scale) as described by Aiken and West (1991). Blockade effect values were then predicted for these representative low and high anger management style values and were plotted by gender. Similar hierarchical regressions were used in preliminary analyses to examine the effects of gender and anger management style on placebo condition pain responses. All probability values reported are two-tailed with a $p < .05$ criterion for significance.

Repetition of the analyses above excluding drug order as a control variable slightly weakened the effects, but left the pattern of significant findings unchanged.

Results

Anger Management Style and Pain Responses by Drug Condition

Zero-order correlations between anger management style measures and both placebo and naltrexone condition pain responses are presented in Table 2. Examination of this table indicates that anger-out was not significantly correlated with pain responses in either drug condition. Although none of these correlations approached significance, correlations with threshold and tolerance were negative and correlations with pain ratings were positive, as would be expected based on prior work. Anger-in displayed a marginally significant positive correlation with placebo PRI pain ratings as anticipated. In contrast, naltrexone condition pain tolerance was positively correlated with anger-in, indicating that across genders and under opioid blockade, elevated anger-in had significant analgesic effects (greater pain tolerance).

To replicate and extend past work not using opioid blockade manipulations, hierarchical regressions were conducted to examine main and interactive effects of anger management style and gender on placebo condition pain responses. These regressions indicated that a main effects model including gender and anger-out accounted for a significant increment in variance accounted for in predicting placebo pain tolerance (R^2 change = .14, F Change = 11.64, $p < .001$). However, this effect was due entirely to female gender predicting significantly lower pain tolerance ($\beta = -.37$, $p < .001$). All main effects of anger-out and gender × anger-out interactions were nonsignificant for placebo NFR threshold, and pain threshold and tolerance, as were all effects in placebo pain rating analyses ($p > .10$).

Table 2 Zero-order correlations between anger management style measures and placebo and naltrexone condition pain responses

Variable	Anger-in	Anger-out
Pain threshold—Placebo	.04	–.07
Pain threshold—Naltrexone	.11	–.08
Pain tolerance—Placebo	–.01	–.08
Pain tolerance—Naltrexone	.17*	–.06
PRI ratings—Placebo	.14**	.03
PRI ratings—Naltrexone	.10	.11
NFR threshold—Placebo	.04	–.11
NFR threshold—Naltrexone	–.13	–.06

*$p < .05$, **$p < .10$

Redundant with the effects above, a main effects regression model including gender and anger-in accounted for a significant increment in variance accounted for in placebo condition pain tolerance (R^2 change = .14, F Change = 11.13, $p < .001$), again due to female gender predicting significantly lower pain tolerance ($\beta = -.38$, $p < .001$). Remaining placebo condition analyses revealed no other significant main or interaction effects of gender or anger-in on placebo NFR threshold, pain threshold or tolerance, or any significant effects for placebo pain ratings ($p > .10$).

Anger Management Style and Opioid Blockade Effects

Anger-out

Results of significant hierarchical regressions for anger-out influences on blockade effects are summarized in Table 3. As noted previously, positive blockade effect values indicate that pain responsiveness increased with naltrexone, providing evidence for opioid-mediated analgesia in the placebo condition. These regressions revealed that a gender × anger-out interaction model produced a significant increment in variance accounted for in pain threshold blockade effects. The source of this interaction was explored via simple effects analyses by gender. As in past work, females displayed a significant negative relationship between anger-out and pain threshold blockade effects ($\beta = -.25$, $p < .05$). Among males, however, anger-out showed a significant positive relationship with pain threshold blockade effects ($\beta = .21$, $p < .05$). Figure 1 presents blockade effect values predicted via regression for hypothetical low and high anger-out values (–1 SD and +1 SD from the mean anger-out scale score) by gender. Inspection of this figure indicates that while female participants showed the expected pattern of diminished opioid analgesic function (i.e., smaller blockade effects) in high anger-outs, male participants exhibited an opposite pattern.

A gender × anger-out model produced a marginally significant increase in variance accounted for in pain tolerance blockade effects as well. Simple effects analyses revealed that this interaction was due to a nonsignificant positive association between anger-out and pain tolerance blockade effects in males ($\beta = .09$, $p \geq .10$) but a nonsignificant negative association in females ($\beta = -.18$, $p \geq .10$). For analyses of blockade effects derived for pain threshold and pain tolerance, all main effects of gender and anger-out were nonsignificant ($p > .10$).

Consistent with pain threshold and tolerance blockade effect results, analyses of blockade effects derived for McGill Pain Questionnaire (PRI) pain ratings revealed a marginally significant gender × anger-out interaction.

Table 3 Summary of hierarchical regression analyses for anger-out and blockade effects

Dependent variable	Step/Predictor variables	Change in R^2 of step	p for change in R^2 of step	B	SE B	p for predictor variable
Pain threshold blockade effects	Step 1:	.31	<.001			
	Drug order			–7.61	.95	<.001
	Step 2:	.01	n.s.			
	Anger-out			.01	.14	n.s.
	Gender			1.22	.97	n.s.
	Step 3:	.05	<.001			
	Anger-out × gender			–.90	.27	<.001
Pain tolerance blockade effects	Step 1:	.05	<.01			
	Drug order			–2.81	1.00	<.01
	Step 2:	.02	n.s.			
	Anger-out			–.10	.15	n.s.
	Gender			–1.49	1.03	n.s.
	Step 3:	.02	<.09			
	Anger-out × gender			–.51	.29	<.09
PRI pain rating blockade effects	Step 1:	.13	<.001			
	Drug order			–3.83	.84	<.001
	Step 2:	.02	n.s.			
	Anger-out			.11	.12	n.s.
	Gender			1.45	.86	n.s.
	Step 3:	.02	<.07			
	Anger-out × gender			–.46	.25	<.07
NFR threshold blockade effects	Step 1:	.05	<.05			
	Drug order			3.66	1.52	<.05
	Step 2:	.02	n.s.			
	Anger-out			–.29	.22	n.s.
	Gender			–.87	1.55	n.s.
	Step 3:	.03	<.08			
	Anger-out × gender			–.79	.44	<.08

Simple effects analyses indicated that this interaction was due to a marginally significant positive association between anger-out and PRI blockade effects in males ($\beta = .20$, $p < .08$), but a nonsignificant negative association in females ($\beta = -.10$, $p \geq .10$).

Analyses of blockade effects derived for NFR threshold also revealed a marginally significant gender × anger-out interaction. Similar to the pain threshold findings above, this interaction was due to a significant negative association in females ($\beta = -.28$, $p < .05$), but a nonsignificant positive association in males ($\beta = .05$, $p > .10$).

Anger-in

Results of significant hierarchical regressions for anger-in influences on blockade effects are summarized in Table 4. Results indicated that a model including the gender × anger-in interaction produced a significant increment in variance accounted for in pain threshold blockade effects. Simple effects analyses by gender indicated that, consistent with anger-out analyses, anger-in and pain threshold blockade effects demonstrated negative and significant associations in female participants ($\beta = -.23$, $p < .05$), but nonsignificant positive associations in male participants ($\beta = .12$, $p \geq .10$). This interaction is portrayed graphically in Fig. 2 for hypothetical high and low anger-in scale values (as above).

Similar analyses indicated that a main effects model including gender and anger-in led to a significant increment in variance accounted for in pain tolerance blockade effects. This effect was due largely to a significant negative association between anger-in and pain tolerance blockade effects. Blockade effect analyses for NFR threshold and pain threshold and tolerance did not reveal any other significant main or interactive effects of gender or anger-in (all $p > .10$). Comparable analyses of pain rating blockade effects also failed to reveal any significant main or interaction effects (all $p > .10$).

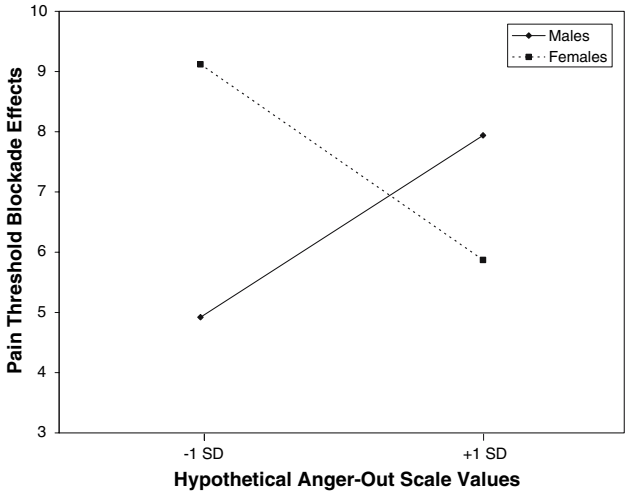

Fig. 1 Effects of anger-out on pain threshold opioid blockade effects in male and female participants. Anger-out values plotted are hypothetical values representing one standard deviation (SD) below and above the sample mean. Larger blockade effects indicate greater opioid analgesia

Overlap between Opioid-related Effects of Anger-in and Anger-out?

Given similar relationships between pain threshold blockade effects and both anger-in and anger-out scores (i.e., high scoring females on both measures demonstrate evidence for opioid dysfunction), additional subgroup analyses in female participants were conducted to explore potential overlap between these effects. Among females, anger-out and anger-in were correlated $r = .25$, $p < .05$. When both anger-in and anger-out were simultaneously included as predictors of pain threshold blockade effects in an hierarchical regression restricted to female participants, this main effects model was significant (R^2 change = .09, F Change = 3.56, $p < .05$). Zero-order correlations associated with this model were then contrasted with analogous semi-partial correlations to test the extent to which anger-in and anger-out effects overlapped. Zero-order correlations indicated that anger-in correlated with pain threshold blockade effects $r = –.32$, with the magnitude of this effect reduced by half when examined as a semi-partial correlation controlling for anger-out ($r = –.16$). In contrast, while the zero-order correlation between anger-out and pain threshold blockade effects was smaller than for anger-in ($r = –.20$), it was essentially unchanged when examined as a semi-partial correlation controlling for anger-in ($r = –.19$). This pattern of findings suggests that while a meaningful portion of the observed relationship between anger-in and opioid function could be accounted for by overlap with anger-out, none of the anger-out/opioid relationship was accounted for by anger-in. As suggested by past work (Bruehl et al. 2002, 2003b, in press), this would appear to indicate that anger-out/opioid links may take precedence over those involving anger-in.

Role of General Negative Affectivity

Both anger-in and anger-out may be associated positively with other general negative affect states, such as depression or anxiety (Beutler et al. 1986; Bruehl et al. 2002; Burns et al. 1996; Tschannen et al. 1992). It is therefore possible

Table 4 Summary of hierarchical regression analyses for anger-in and blockade effects

Dependent variable	Step/predictor variables	Change in R^2 of step	p for change in R^2 of step	B	SE B	p for predictor variable
Pain threshold blockade effects	Step 1:	.31	<.001			
	Drug order			–7.61	.95	<.001
	Step 2:	.01	n.s.			
	Anger-in			–.03	.13	n.s.
	Gender			1.21	.97	n.s.
	Step 3:	.02	<.05			
	Anger-in × gender			–.52	.26	<.05
Pain tolerance blockade effects	Step 1:	.05	<.01			
	Drug order			–2.81	1.01	<.01
	Step 2:	.08	<.01			
	Anger-in			–.44	.14	<.01
	Gender			–1.61	.96	n.s.
	Step 3:	.00	n.s.			
	Anger-in × gender			.07	.28	n.s.

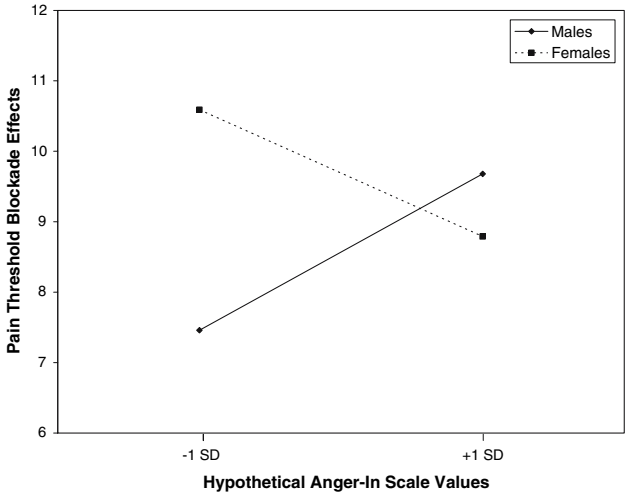

Fig. 2 Effects of anger-in on pain threshold opioid blockade effects in male and female participants for hypothetical high and low anger-in values

that associations between measures of opioid function and both anger-in and anger-out in the current study might not reflect unique effects of anger management style, but rather the effects of shared variance with general negative affect.

The measures of anxiety and depression that were obtained permitted several analyses to address potential influences of general negative affect on the pattern of findings. First, zero-order correlations revealed that anger-out was modestly but nonsignificantly correlated with trait anxiety in the expected direction ($r = .13$, $p < .14$), but had little relationship with depression scores ($r = .04$, $p > .10$). Anger-in showed virtually no relationship with either trait anxiety ($r = .03$, $p > .10$) or depression scores ($r = –.05$, $p > .10$). Next, significant blockade effect regression analyses above were repeated, entering both trait anxiety and depression scores in the step prior to entry of the gender and anger management style effects of interest. These analyses indicated that after controlling for depression and anxiety, the gender × anger-out interaction continued to be a significant predictor of pain threshold blockade effects (incremental R^2 change = .05, $p < .05$), with a similar marginally significant effect for pain tolerance blockade effects (incremental R^2 change = .02, $p < .10$). The nature of these interactions was unchanged. The main effects model including gender and anger-in for predicting pain tolerance blockade effects remained significant after controlling for general negative affect (incremental R^2 change = .07, $p < .01$), and the gender × anger-in interaction as a predictor of pain threshold blockade effects was only slightly reduced (incremental R^2 change = .02, $p < .07$). Inspection of the results of the original analyses in Tables 3 and 4 indicates that controlling for negative affect in the models examined left the incremental variance accounted for in each analysis essentially unchanged. These findings suggest that the relationships between opioid blockade responses and both anger-in and anger-out may be due to a specific link between opioids and anger management style rather than negative affect in general.

Discussion

Prior work suggests that the often-reported hyperalgesic effects of elevated trait anger-out may be due in part to dysfunctional endogenous opioid analgesic activity (Bruehl et al. 2002, 2003b, in press). The findings of the current study provide partial support for this opioid dysfunction hypothesis, confirming that elevated anger-out is associated with reduced endogenous opioid analgesia in healthy female participants. In contrast, for males, elevated anger-out was associated with somewhat greater opioid analgesia. The fact that gender appeared to moderate anger-out/opioid relationships is not entirely unexpected, given evidence in past work that gender may moderate the relationship between anger-out and pain responses (Burns et al. 1996; 1998), cardiovascular responses (Bongard and al'Absi 2005; Faber and Burns 1996), and paraspinal muscle reactivity (Burns 1997). While results of studies examining pain outcomes led us to anticipate possible gender moderation, the limited and somewhat contradictory nature of this earlier work did not permit specific directional hypotheses to be generated regarding opioid effects. For example, results of Burns et al. (1998) suggested that males but not females exhibited hyperalgesia related to anger-out (as indexed by smaller improvement in lifting capacity with chronic pain treatment). In contrast, Burns et al. (1996) found that elevated anger-out (in combination with high hostility) was associated with hyperalgesia in female chronic pain patients, but with relatively lower chronic pain intensity in males patients. Findings in the current study of an association between elevated anger-out and diminished opioid analgesia in females but greater opioid analgesia in males would appear to be most consistent with the latter study. The fact that no studies other than those above have explicitly examined gender moderation effects regarding relationships between anger-out and pain outcomes or opioids leaves open the question of whether these effects are spurious (sample dependent) or reflect real differences; replication is required.

It should be noted that previous experimental tests demonstrating links between elevated anger-out and opioid dysfunction found no evidence of gender main effects on opioid outcomes, and that results that were reported reflected statistical control of gender-related differences

(Bruehl et al. 2002, in press). Gender interactions were not explicitly tested previously in part due to relatively small sample sizes for testing interactions and unequal gender distribution in our samples (e.g., 58% of controls and 66% of chronic pain participants were female in Bruehl et al. 2002). The predominately female gender distribution in this prior opioid blockade work may account for the fact that overall main effects for anger-out in that study indicated an association with opioid dysfunction. It is unknown to what extent inclusion of a chronic back pain subgroup (in whom opioid function may be altered) in analyses reported in this prior work may also have contributed to the observed pattern of findings independent of gender issues. The current study is the first to explicitly test for gender moderation of associations between opioid function and anger management style, and the positive findings suggest that such issues may be important to consider in future work.

A notable difference between results of the current study and past related work is the finding regarding anger-in. Previous studies using both opioid blockade and assessment of plasma endogenous opioids demonstrated virtually no evidence of associations between anger-in and opioid function (Bruehl et al. 2002, in press). In contrast, the current results revealed associations between elevated anger-in and opioid dysfunction for both pain threshold blockade effects (in females) and for pain tolerance blockade effects (across genders). The direction of these effects is consistent with findings that elevated trait anger-in, like anger-out, is often associated with hyperalgesia (Bruehl et al. 2002, Burns et al. 2004, Gelkopf 1997; Kerns et al. 1994). Given that both anger-in and anger-out demonstrated similar patterns of relationships with opioid function, possible overlap between these effects was investigated. Analyses suggested that a substantial portion of the anger-in/opioid association was accounted for by statistical overlap with anger-out, whereas the converse was not found to be true. Thus, while the findings of associations between anger-in and opioid dysfunction in the current study are novel, their interpretation must be tempered by the possibility that this effect may not be independent of previously reported anger-out/opioid associations.

Another question addressed in this study is whether associations between anger management style and endogenous opioid analgesia reflect unique contributions of anger management style, or simple overlaps with general negative affect. This possibility was suggested by reports that both anger-in and anger-out may be associated positively with other general negative affect states, such as depression or anxiety (Beutler et al. 1986; Bruehl et al. 2002; Burns et al. 1996; Tschannen et al. 1992). In the current study, neither of these anger management style measures was associated significantly with measures of depression or anxiety, nor were their associations with opioid analgesia altered by statistical control of these negative affect variables. These findings suggest that observed relationships between opioid function and both anger-in and anger-out were not attributable to overlapping variance with general negative affect, but were more likely specific to anger regulation styles.

Several potential study limitations should be considered. While the gender moderation effects described above are intriguing, their interpretation in the current study is not entirely straightforward. Specifically, although associations were found between opioid function and anger-out as expected, associations between anger-out (as well as anger-in) and placebo pain responses were weaker than anticipated. Reasons for the relative absence of placebo condition effects are not clear. It is possible that the nature of the pain stimulus used may be one contributor. To our knowledge, the current study is the first to examine the issue of anger management style-related hyperalgesia using an electrocutaneous acute pain stimulus. Whatever the cause, results do indicate significant associations between anger-out and degree to which acute pain responses are modulated by endogenous opioids, even if their impact on actual pain responses in this study is not entirely clear. Further replication of these findings would be desirable.

Another potential limitation is carryover effects. In both drug conditions, electrocutaneous pain threshold and tolerance were determined following a series of three trials assessing NFR threshold. It is possible that the stimulation during these NFR trials affected the pain responses during subsequent pain threshold and tolerance trials. This is another possible contributor to the absence of expected placebo condition effects, although no data are available to evaluate this possibility empirically.

An additional potential interpretive issue is with regard to the magnitude of the blockade effects. Table 1 indicates that opioid blockade had little systematic effect on pain responses when influences of anger management style were ignored. This finding is similar to our previous work (Bruehl et al. 2002), which also showed that mean overall opioid blockade effects were not statistically different from zero when anger expression measures were disregarded. The key point, however, is that individuals higher in anger-out (and specifically females in the current study) are more likely to be in the subgroup reporting no change or decreased pain with blockade, whereas low anger-outs are more likely to report the expected increase in pain with opioid blockade. One might predict that manipulations inducing increased arousal (e.g., harassment) that could trigger opioid release would increase the overall magnitude of blockade effects on subsequent pain tasks. Whether this is the case, and whether such manipulations magnify

differences in opioid function between those higher and lower in anger-out, is the subject of current investigations in our lab.

In a related vein, the degree of influence of drug administration order on magnitude of blockade effects in the current study was notable. Participants receiving opioid blockade the first session reported significantly larger blockade effects on pain responses. As suggested in the discussion above, this most likely reflects the interaction of opioid blockade with elevated baseline arousal levels due to the novelty of the first experimental session.

Finally, it should be noted that while there were several significant effects as expected, the magnitude of these in terms of variance accounted for was rather small (2–5% of blockade effect variance for gender × anger-out interactions). Effects in the current study were smaller than those noted for anger-out in our prior work in which main effects of anger-out accounted for as much as 12% of the variance in opioid-mediated analgesia (Bruehl et al. 2002). Reasons for these discrepancies are not known, but may include methodological differences such as type of opioid blockade agent (intravenous naloxone versus oral naltrexone) and nature of the acute pain stimuli (finger pressure and ischemic pain tasks versus electrocutaneous pain).

In summary, including the current findings, associations between elevated trait anger-out and opioid dysfunction have now been observed in three independent samples using multiple pain stimuli (thermal, finger pressure, ischemic, and electrocutenous) and opioid indices (plasma opioid levels, pharmacological opioid blockade with naloxone and naltrexone), supporting the validity of the effect. Additional work is required to better understand the moderating effects of gender and situational parameters (e.g., actual anger expressive behavior) on these opioid effects.

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