ORIGINAL ARTICLE

Brain Response to Empathy-Eliciting Scenarios Involving Pain in Incarcerated Individuals With Psychopathy

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Importance: A marked lack of empathy is a hallmark characteristic of individuals with psychopathy. However, neural processes associated with empathic processing have not yet been directly examined in psychopathy, especially in response to the perception of other people in pain and distress.

Objective: To identify potential differences in patterns of neural activity in incarcerated individuals with psychopathy and incarcerated persons serving as controls during the perception of empathy-eliciting stimuli depicting other people experiencing pain.

Design: In a case-control study, brain activation patterns elicited by dynamic stimuli depicting individuals being harmed and facial expressions of pain were compared between incarcerated individuals with psychopathy and incarcerated controls.

Setting: Participants were scanned on the grounds of a correctional facility using the Mind Research Network's mobile 1.5-T magnetic resonance imaging system.

Participants: Eighty incarcerated men were classified according to scores on the Hare Psychopathy Checklist–Revised (PCL-R) as high (27 men; PCL-R, ≥30), intermediate (28 men; PCL-R, 21-29), or low (25 men; PCL-R, ≤20) levels of psychopathy.

Main Outcome Measure: Neurohemodynamic response to empathy-eliciting dynamic scenarios revealed by functional magnetic resonance imaging.

Results: Participants in the psychopathy group exhibited significantly less activation in the ventromedial prefrontal cortex, lateral orbitofrontal cortex, and periaqueductal gray relative to controls but showed greater activation in the insula, which was positively correlated with scores on both PCL-R factors 1 and 2.

Conclusions and Relevance: In response to pain and distress cues expressed by others, individuals with psychopathy exhibit deficits in the ventromedial prefrontal cortex and orbitofrontal cortex regardless of stimulus type and display selective impairment in processing facial cues of distress in regions associated with cognitive mentalizing. A better understanding of the neural responses to empathy-eliciting stimuli in psychopathy is necessary to inform intervention programs.

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PSYCHOPATHY IS A PERSONALITY disorder characterized by affective and interpersonal deficits as well as social deviance and poor behavioral control. As measured by the Hare Psychopathy Checklist–Revised (PCL-R),[1] psychopathy comprises interpersonal, affective (factor 1), and lifestyle and antisocial (factor 2) features. The interpersonal/affective component of psychopathy is largely defined by a lack of empathy and attachment, as well as a callous lack of regard for others.[2] Empathy, the natural capacity to share and understand the affective states of others,[3] is at the heart of the first of the disorder's 2 core components.

The construct of empathy is complex and involves social, emotional, and motivational facets.[3-5] The primary component of empathy, empathic sensitivity (or empathic arousal), refers to the automatic sharing of the affective states of others and is a crucial prerequisite to the experience of empathic concern (ie, other-oriented emotional response congruent with the perceived welfare of someone in need).[4] Interconnected subcortical regions, including the brainstem, amygdala, and hypothalamus, and cortical regions such as the insula, orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (vmPFC), form the essential neural circuit of empathy.[3-5] Empathic sensitivity is a phylogenetically ancient and basic form of intraspecies communication, and it is the first component of empathy to develop in children.[4,6,7] The vi-

carious sharing of another's negative state provides a strong signal that can promote empathic concern, and the lack of such signals during development can impede the process of normal socialization.[7,8] To be motivated to help another, one needs to be affectively, empathically aroused and anticipate the cessation of mutually experienced personal distress.[9,10] Empathic sensitivity may thus serve as a catalyst in promoting empathic concern for others: the lack of this signal would make the engagement of empathic concern and prosocial behavior much less likely.[4,11]

The perception of others' pain or physical distress usually acts as a prosocial signal, notifying others that their conspecific is at risk, attracting their attention, and motivating helping behavior,[12] and has become a fruitful avenue to investigate the neural mechanisms underpinning affective processing and empathy.[13]

In healthy participants, functional magnetic resonance imaging (fMRI) studies[6,8,13-19] of empathy have demonstrated reliable activation of a neural network that overlaps substantially with regions engaged when one experiences pain and when one perceives, anticipates, or even imagines pain happening to others. The activated neural network includes the anterior insular cortex (AIC), dorsal anterior cingulate cortex (dACC), anterior midcingulate cortex (aMCC), supplementary motor area (SMA), somatosensory cortex, amygdala, periaqueductal gray, and vmPFC.[20]

The neural response to the distress of others, such as pain, is thought to reflect an aversive response in the observer that may act as a trigger to inhibit aggression or prompt motivation to help.[3-8] Hence, examining the neural response of individuals with psychopathy as they view others being hurt or expressing pain may be an effective probe into the neural processes underlying affective and empathic deficits in psychopathy.

To date, no fMRI study has investigated the neural response to empathy-eliciting stimuli in incarcerated individuals with psychopathy. Previous research[21-23] showed that these people understand the emotional state of others without "sharing" their feelings or being aroused by their emotional states. Thus, one can anticipate different hemodynamic response in the neural network involved in the perception of pain between individuals with psychopathy, especially for participants scoring high on the PCL-R. An alternative hypothesis draws on research showing that children and adolescents with callous-unemotional traits are reward-oriented, insensitive to punishment cues, lack emotional responsiveness to distress cues, and may show both reactive and instrumental aggression.[24] In support of this hypothesis, one study[23] found that male adolescent offenders with high callous-unemotional traits exhibited atypical neural dynamics of pain empathy processing (measured with event-related brain potentials) in the early stages of affective arousal coupled with relative insensitivity to actual pain. Another neuroimaging study[25] documented strong activation of the amygdala (as well as the pain network), which correlated with a measure of sadism, in youth with aggressive conduct disorder when they observed people being hurt.

To investigate the neural mechanisms underlying empathy for pain in adults with psychopathy, 80 incarcerated male volunteers, stratified into 3 groups, were scanned using fMRI. Participants classified as having a high level of psychopathy (n=27) were those who scored 30 or above on the PCL-R (of a possible 40), those classified as having intermediate psychopathy (n=28) scored between 21 and 29, and volunteers scoring 20 or below (n=25) were classified as low-psychopathy controls. Well-matched groups from the prison population are used to isolate differences due to psychopathy and eliminate confounding factors possible in the direct comparison of incarcerated people with psychopathy with community controls.

Furthermore, the inclusion of participants from across the scoring spectrum allowed us to investigate differences at a groupwise and a continuous level using both PCL-R total and factor 1 and 2 scores. The neurohemodynamic activity was measured while participants attended to visual scenarios depicting individuals being physically hurt and dynamic facial expressions of pain; these stimuli have been used in numerous fMRI studies[6,8,13-19,23,25-30] investigating the neural underpinnings of empathy for pain in healthy children, adolescents, and adults. Moreover, having 2 sets of stimuli, ie, pain interactions (2 persons interacting without the faces of the protagonists) and facial expressions of pain may help us identify which component of empathy is dysfunctional in psychopathy. The former class of stimuli requires a cognitive understanding of a social interaction with a negative outcome, which is associated with the engagement of the network supporting mental state inference and the perception of pain in others[8]; the latter also induces activation in the OFC and vmPFC, which are prefrontal regions that play a pivotal role in adaptive responses to emotionally relevant situations and the production of an affective state.[31,32]

METHODS

PARTICIPANTS

Eighty men (aged 18-50 years) incarcerated in a medium-security North American correctional facility volunteered for the research study and provided informed consent for the procedures described herein, which were approved by the institutional review boards of the University of New Mexico and The University of Chicago. Volunteers underwent the PCL-R, including file review and interview, conducted by trained research assistants under the supervision of one of us (K.A.K.). Those scoring 30 and above on the PCL-R were assigned to the high-psychopathy group (n=27). To create the low- and medium-psychopathy groups, 2 groups of volunteers were matched to high scorers on age, race, and ethnicity, IQ, comorbidity for *DSM-IV* Axis II disorders,[1,33] and past drug abuse and dependence from those scoring at or below 20 on the PCL-R (n=28) and volunteers scoring between 21 and 29 (n=25), respectively. The sample size for each group was determined by a power analyses based on prior studies.[34] Participants were paid $1 per hour, which is a typical rate for institutional labor compensation.

MRI ACQUISITION

Scanning was conducted on a 1.5-T mobile MRI unit (Magnetom Avanto; Siemens Healthcare) equipped with advanced susceptibility quantification gradients and a 12-element head

Figure 1. Tasks used to example neural processes involved in empathy. A, An example of the last frame of the pain interactions task. In this task, 48 visual scenarios depicting pain and 48 control scenarios without pain were used. Each scenario consisted of a 3-part frame capture taken from videos of live actors, presented at the rate of 1000, 200, and 1000 milliseconds to simulate biological motion. The scenarios depicted people intentionally harming another person by actions such as striking, cutting, pinching, or crushing that person's hands, feet, arms, legs, fingers, or toes. Control stimuli included sequences in which 2 people interacted, but no harm or pain occurred. No heads or faces were visible in the scenarios. Data were collected in 2 runs, with each 7 minutes. B, An example of the pain expression task. Video clips showed a natural pain response in which individuals displayed brow lowering, orbit tightening, and either pursing/pressing of the lips or opening/stretching of the mouth. These movements have consistently been attributed to the facial expression of pain. After 8 of the clips were shown, participants were asked whether the previous clip had featured a male or a female. Data in this task were acquired in one 8-minute run.

coil. Functional images were collected using an echo planar imaging gradient-echo pulse sequence with repetition time/echo time, 2000/39 milliseconds; flip angle, 90°; field of view, 240 × 240 mm; matrix, 64 × 64 cm; in-plane resolution, 3.4 × 3.4 mm; slice thickness, 5 mm; and 30 slices, full-brain coverage. Task presentation was implemented using commercial software (E-Prime, Psychology Software Tools Inc).

High-resolution T1-weighted structural MRI scans were acquired using a multiecho magnetization-prepared rapid gradient echo pulse sequence (repetition time, 2530 milliseconds; echo times, 1.64, 3.50, 5.36, and 7.22 milliseconds; inversion time, 1100 milliseconds, flip angle, 7°; slice thickness, 1.3 mm; matrix size, 256 × 256) yielding 128 sagittal slices with an in-plane resolution of 1.0 × 1.0 mm.

TASK DESIGN

Participants completed 2 counterbalanced tasks to examine neural processes involved in empathy through observation of individuals experiencing pain. One task was designed to assess the neural response to visual scenarios depicting physical harm; the other task measured the neural activity to viewing facial expressions of pain.

PAIN INTERACTIONS TASK

In this task, used previously in several fMRI studies,[6,8,14,25] participants viewed 96 short dynamic visual stimuli depicting persons harming one another, presented in a pseudorandomized rapid event-related design (**Figure 1**A). Timing parameters were generated using Optimize Design.[35] To verify the participants' attention to the task, 8 randomized trials were followed with the question, "Did a person in the previous picture feel pain?" The participant then had 6 seconds to answer the question by pressing the correct button.

PAIN EXPRESSIONS TASK

The second functional task examined neural responses during the viewing of dynamic facial expressions of pain (Figure 1B). Participants were presented with 64 video clips of expression stimuli 2.2 seconds in duration, interspersed with 32 instances of a dynamically scrambled baseline stimulus.

IMAGE PROCESSING AND ANALYSIS

The functional images were processed using SPM8 (Wellcome Department of Imaging Neuroscience) in technical computing software (Matlab; MathWorks Inc). For each participant, functional data were realigned to the first image acquisition of the series and resampled to a voxel size of 2 × 2 × 2 mm. Structural T1 images were coregistered to the mean functional image and segmented using the new segment routine. A group-level structural template and individual flow fields were created using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), and the flow fields were in turn used to spatially normalize functional images to standard Montreal Neurological Institute space. Data were smoothed with an 8-mm full-width at half maximum isotropic gaussian kernel. Ten participants were eliminated from further analysis because of image quality issues related to movement or image quality, leaving 70 for analysis (22, 24, and 24 for low, intermediate, and high psychopathy, respectively).

Statistics were calculated at the first level using the general linear model. The design matrix included 3 regressors for each stimulus category (detailed above), representing the event onsets and their time and dispersion derivatives. Movement parameters from the realignment output were included as regressors of no interest. All participants were entered into 2 second-level pooled analyses (1 for the pain interactions task and 1 for the pain expressions task), and full brain results are reported at a statistical cutoff of familywise error–corrected $P < .05$.

Second-level analyses were conducted by comparing the extremes of the sample distribution of PCL-R scores and then as a continuous regressor using the entire sample. Participants with PCL-R total scores of 30 or more were selected for the psychopathy group, while participants scoring 20 or below composed the incarcerated control group. For these analyses, regions of interest were created from the existing literature. For the pain interactions task, coordinates for regions of interest were taken from previous fMRI studies[6,8,14,25] that used the same task paradigm used here and from a meta-analysis of 32 fMRI studies of empathy for pain.[20] For the pain expressions task, coordinates were taken from studies[27-30,36,37] that reported functional neuroimaging results for the perception of facial expressions of pain. Region of interest data

are reported for significant contrast image peaks within 8 mm of these a priori coordinates. In addition to existing information on the processing of empathy-inducing stimuli in healthy populations, there may be cortical or subcortical brain regions that contribute to abnormal processing of these regions in psychopathy. For this reason, further regions of note that survived the statistical cutoff of $P < .001$ uncorrected and a spatial extent threshold of k = 100 voxels are also reported in the groupwise analysis.

To explore whether results found in the groupwise analysis may be the result of PCL-R factor 1, factor 2, or both, the regions reported in the meta-analysis[20] were tested for significant correlation with PCL-R factor scores. Corresponding *t* values for subfactor covariates within 5 mm of the regions of interest analyzed, if significant, are reported for each factor and task.

RESULTS

Regions of interest for all tasks are reported in eTable 1 (http://www.jamapsych.com). Additional detailed results are included as Author Tables where noted (available from the author by request).

PERCEIVING PAIN INTERACTIONS

When participants viewed dynamic stimuli depicting individuals being physically injured, significant signal increase was detected in several clusters surviving a statistical cutoff of familywise error–corrected $P < .05$, which were located bilaterally in the AIC, dACC, aMCC, SMA, supramarginal gyrus, inferior parietal lobule (IPL), precuneus, and posterior cingulate gyrus. Significant subcortical activations were also seen bilaterally in the thalamus and globus pallidus. At a slightly relaxed cutoff of $P < .0001$ with a spatial extent threshold of k = 100 voxels, additional activations were seen in the amygdala, OFC, and vmPFC (Author Table 1 for full results).

Participants from within the pooled analysis were selected from the extremes of the PCL-R total score distribution to compose psychopathy (PCL-R score, ≥30) and control (PCL-R score, ≤20) groups. At a cutoff threshold of $P < .05$, corrected for familywise error for a priori regions of interest, control participants had greater activation in the periaqueductal gray, vmPFC, and lateral OFC (Author Table 2). High-scoring individuals with psychopathy exhibited greater activation in a priori regions including the SMA, dACC, bilateral AIC, dorsal striatum, inferior frontal gyrus (IFG), medial prefrontal cortex, posterior superior temporal sulcus (pSTS), postcentral gyrus, and supramarginal gyrus (Author Table 3).

CORRELATIONS WITH PCL-R

To examine the extent to which the results seen in the groupwise comparison were driven by scores on factor 1 (representing deficits in affective and interpersonal components) or factor 2 (measuring deficits in behavioral controls and impulsivity) of the PCL-R, each cluster was tested for significant correlations with PCL-R factor scores. For clusters more active in the control group, 3 were significantly negatively correlated with both factor scores: periaqueductal gray, the vmPFC, and the superior temporal pole. Activity in the lateral OFC was not significantly correlated with either factor score (Author Table 4).

For clusters found to be significantly more active in the psychopathy group, several were significantly correlated with both factor scores, including the right AIC, right IFG, right pSTS, right superior frontal gyrus, right dorsomedial prefrontal cortex (dmPFC), and left precuneus. Several clusters were correlated only with factor 1 scores (but not significantly correlated with factor 2 scores), including the right SMA, bilateral dACC, bilateral dorsal striatum, IFG, and somatosensory cortex (Author Table 5).

PERCEIVING FACIAL EXPRESSIONS OF PAIN

In the pain expressions task, participants showed robust hemodynamic activation in the face network of expected cortical and subcortical brain regions during the perception of facial expression of pain.[38] At the full-group level (n = 70), clusters (familywise error–corrected $P < .05$) were detected bilaterally in the fusiform gyrus, occipital regions, pSTS, and IFG. At a slightly relaxed cutoff of $P < .0001$ with a spatial extent threshold of k = 100 voxels, additional activations were seen bilaterally in the AIC, aMCC, right hemisphere parietal regions, thalamus, and striatum (Author Table 6 for full results).

In direct comparison between groups, control participants had greater activation bilaterally in the IFG, middle cingulate cortex, angular gyrus, putamen, pSTS, supramarginal gyrus, dmPFC, globus pallidus, and dACC. At a relaxed whole-brain uncorrected cutoff of $P < .001$, additional clusters of greater activation in the control group were observed in the vmPFC and medial OFC (Author Table 7). Individuals with psychopathy exhibited greater activation in a priori regions in the AIC, postcentral gyrus, IPL, and precentral gyrus (Author Table 8).

PCL-R CORRELATIONS

Several clusters found to be significantly more active in the control group, including the middle cingulate cortex, IFG, dmPFC, and left angular gyrus, were negatively correlated with factor 1 and 2 scores. The right angular gyrus and left pSTS were correlated only with factor 1, and the right STS, dACC, and striatum were correlated only with factor 2 (Author Table 9). In the reverse direction, activity in the AIC was positively correlated with both factor 1 and 2 scores. Two clusters from the left postcentral gyrus and right precentral gyrus were correlated only with factor 1 scores (Author Table 10).

BETWEEN-TASK COMPARISONS

Two regions (left postcentral gyrus and right precentral gyrus) were congruent, between tasks, in the direction of differences between psychopaths and controls, and 4 others were different but task-dependent. Individuals with psychopathy had significantly greater activation in the AIC than did controls while viewing others in pain, whether the pain was in the form of facial expressions or people interacting (**Figure 2**). Controls, conversely,

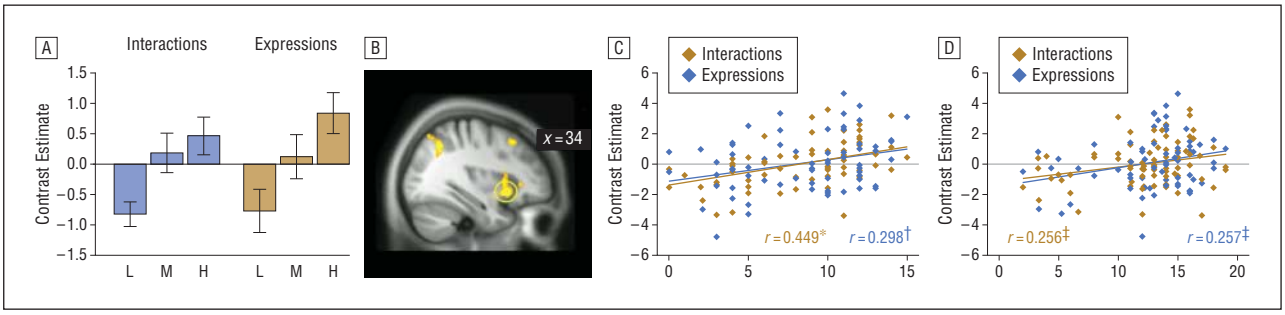

Figure 2. Groupwise and continuous measures of hemodynamic response in the right anterior insular cortex. Blood oxygen level dependence response increased as a function of the degree of psychopathy (as measured by the Hare Psychopathy Checklist–Revised [PCL-R]) during the viewing of both types of empathy-eliciting stimuli, interactions in which one person caused pain to another (interactions) and facial expressions of pain (expressions). A, Histogram of responses of all participants stratified into 3 groups. B, Anatomical location of cluster of interest (circled) superimposed on the sample-specific diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL)–normalized T1 template at Montreal Neurological Institute (MNI) coordinate x = 34. C and D, The groupwise effects seen in part A were expanded to examine the contribution of continuous factor 1 and factor 2 PCL-R subscores, representing the affective/interpersonal and lifestyle/behavioral features of psychopathy, respectively. Values used for A, C, and D are the contrast estimates per participant averaged across the 3-mm sphere centered on the cluster peak at MNI coordinates (26, 28, −8), from the contrast of scenarios with pain/harm content vs scenarios with no pain/harm in the pain interactions task, and from the contrast of dynamic pain expressions vs dynamic baseline stimuli in the pain expressions task. Error bars indicate the standard error of the mean. H indicates high psychopathy (PCL-R, ≥30); L, low psychopathy (PCL-R, ≤20); and M, intermediate psychopathy (PCL-R, 21-29). *$P<.001$. †$P<.01$. ‡$P<.05$.

had greater activation than did those in the psychopathy group during each task in the right vmPFC and the right lateral OFC (**Figure 3**). In addition, 4 regions were more active in psychopathic individuals for painful interactions but more active in controls for facial expressions of pain. This pattern was observed in the dmPFC, angular gyrus, pSTS, and IFG (eFigure).

DISCUSSION

To better understand the deficits in socioemotional information processing in individuals with psychopathy, the current study used 2 classes of stimuli that have been extensively applied during the past decade to chart the neural network underpinning empathy in healthy adults and children.[6,8,13,14,27-30]

In the pooled analyses of all 70 participants analyzed, collapsed across PCL-R scores, expected patterns of activation were observed during perception of people being hurt and facial expressions of pain. The former elicited activity in the AIC, dACC, aMCC, amygdala, and SMA, and the latter recruited activity in the fusiform gyrus, AIC, pSTS, and IFG.

There were significant differences, however, in several brain regions engaged between the 2 extreme groups. When viewing people being hurt, individuals with psychopathy showed greater activation in the AIC, as well as in the dorsal striatum, dmPFC, and pSTS, 3 regions involved in the cognitive dimension of mentalizing.[39] Control participants showed greater signal increase in the periaqueductal gray, vmPFC, and lateral OFC, a circuit with reciprocal connections with the amygdala and hypothalamus involved in the regulation and mediation of emotional and affective behavior.[9,10]

When viewing facial expressions of pain, fusiform gyrus activity was equivalent between groups. The high-scoring psychopathy group again displayed greater activation bilaterally in the AIC. However, in this case, low-scoring incarcerated control participants had greater activation than those with psychopathy in regions involved in emotional and cognitive aspects of mentalizing, including the vmPFC, OFC, pSTS, dmPFC, IPL, dACC, and dorsal striatum.

The amplified involvement of the AIC in participants with psychopathy is surprising because of the well-documented role of this region in the experience of empathy (Figure 2). The AIC is a polysensory cortex involved in mapping internal states of bodily and subjective feeling. With extensive reciprocal connections with limbic forebrain areas,[40] it is the most consistently activated region across all studies of empathy for pain,[20] even when there is no explicit cognitive demand to empathize with another individual.[41] Moreover, gray matter reduction has been observed in the insula in individuals scoring high on psychopathy tests,[42] although the stereotaxic coordinates are different between their study and ours (posterior insula vs anterior insula, respectively). A previous fMRI study[25] of empathy in children with aggressive conduct disorder and psychopathic tendencies, using similar stimuli, reported similar findings. Increased activity was detected in the AIC as well as reduced response in the OFC when children with conduct disorder were presented with stimuli depicting others in pain. A recent case study[43] reported on a patient who, despite complete destruction of the insula, experienced all aspects of feelings and emotions, including empathy. This indicates that the role of the insula in emotion and empathy is complex and far from being understood. In addition, it has been proposed from network analysis that the insula and ACC form the core of a network that facilitates the detection of important environmental stimuli.[44] The pSTS and medial prefrontal cortex are part of the cognitive mentalizing network (processing intentions and understanding social interaction) and have been reported in previous research using similar stimuli.[8,14] The augmented involvement of these regions, including the AIC, in individuals with psychopathy supports a cognitive assessment strategy of these scenarios rather than an affective processing.

Relative to participants with psychopathy, controls showed greater activation in the OFC and vmPFC when perceiving individuals being injured as well as during facial expressions of pain (Figure 3). This result is in agreement with the affective neuroscience literature on psychopathy. These regions, important for monitoring ongoing behavior, estimating consequences, and incorporating emotional learning into decision making, have consistently been featured in theories of psychopathy and remain the most common prefrontal regions implicated in neuroimaging investigations of the condition.[21,22] Structural and functional deficits in the vmPFC and OFC have been reported[21,22,44-48] in individuals with high psychopathic traits and criminal convictions. The fundamental role of the OFC in empathy is supported by fMRI studies of healthy children[6,8,49,50] and adults,[20,51] and by brain lesions in patients with neurologic disorders.[31,32,52,53] Of particular interest, one recent study[54] examined affective vs cognitive theory of mind processing in criminal offenders with antisocial personality disorder with high psychopathy features as well as in participants with localized lesions in the OFC or dorsolateral prefrontal cortex. The authors found that individuals with psychopathy and those with OFC lesions were impaired on the affective but not cognitive dimension of theory of mind.

Major task-dependent differences were found between groups in 4 brain regions (eFigure). The dmPFC, IPL, pSTS, and IFG were significantly less active during the viewing of facial expressions of pain in the psychopathy group, but significantly more active than in controls while watching individuals hurting others. According to one network model,[39] ventral regions such as the OFC and vmPFC are recruited to process affective aspects of mentalizing, while dorsal regions such as the dmPFC, ACC, and dorsal striatum are recruited for cognitive mentalizing, and the pSTS and IPL are engaged in both aspects of mentalizing. When dealing with either faces or social interactions, empathy-eliciting stimuli led to a significantly dampened response in the affective mentalizing regions in the psychopathy group. However, cognitive mentalizing areas were selectively impaired only in the faces task. This pattern of results suggests not an overall deficit in the theory of mind network but rather a stimulus class-specific failure of this network to be triggered by facial expressions of pain.

There were differential contributions of PCL-R factor 1 and factor 2 scores to the differences uncovered in the groupwise analysis. In previous research,[34] PCL-R factors 1 and 2 have been demonstrated to differentially contribute to abnormalities in brain function in functional imaging assessments of criminals with psychopathy. In the present study, clusters that were more active in the control group than the psychopathy group were generally correlated either with both factor scores or only with factor 2 scores. Conversely, clusters that were more active in the psychopathy group were influenced mainly by factor 1 scores. Furthermore, between the 2 tasks used in the current investigation, the direction of differences between groups was unequally distributed. When looking at facial expressions of pain, the bulk of differences seen between groups were deficits in the psychopathy group and were driven to a greater extent by factor 2,

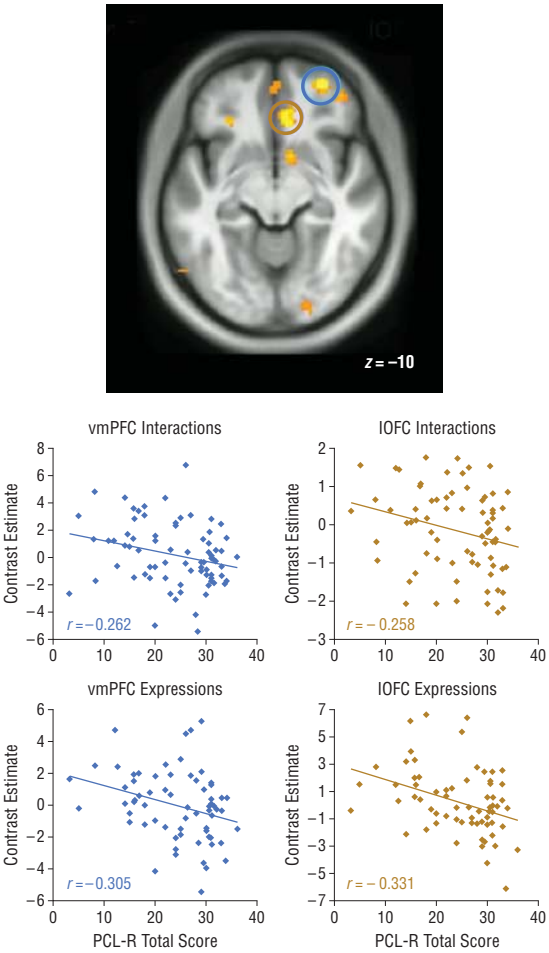

Figure 3. Neurohemodynamic activity in the ventromedial prefrontal cortex (vmPFC) and lateral orbitofrontal cortex (lOFC) decreases as a function of total psychopathy score during the viewing of 2 types of empathy-eliciting stimuli, interactions in which one person caused pain in another (interactions) and facial expressions of pain (expressions). At the center, the clusters illustrated in the figure are indicated on the study-specific T1 template, circled in violet for the vmPFC and blue for the lOFC. At left and right, per-subject contrast estimates averaged across the 3-mm sphere surrounding the peak voxel in each cluster (Montreal Neurological Institute [8, 30, −10] for the vmPFC and [42, 48, −12] for the lOFC) are expanded for the entire sample (N=70) as a function of the Hare Psychopathy Checklist–Revised (PCL-R) total score.

whereas when participants were looking at pain interactions, the bulk of the differences observed were in the direction of greater activation in the psychopathy group, and these differences were driven to a greater extent by factor 1. This is particularly interesting in light of research regarding the relationship of factor 1 scores with instrumental aggression in psychopathy.[55] Instrumental or predatory aggression is controlled, purposeful aggression used to attain a desired external goal. In multiple studies involving adults and adolescents with psychopathy, instrumental aggression has been linked more strongly to factor 1 scores on psychopathy than to factor 2 scores.[56,57] Factor 1 items include conning and manipulation, lying, glibness, and superficial charm, skills with which individuals with psychopathy may achieve external goals through selfish interactions with others.

Thus, greater factor 1–related activity when watching social interactions resulting in harm may reflect a propensity for or interest in this type of behavior. Facial expressions of pain, devoid of any additional contextual information, may not be sufficient to engage similar patterns of processing. Hence, in the pain expressions task used in the current study, the pattern of deficits in the psychopathy group related to both factors or to factor 2 alone may be a purer measure of deficits in empathic sensitivity.

Overall, the results of this study indicate that the major difference in the pattern of brain response between participants with psychopathy compared with controls during the perception of others in pain is the lack of engagement of regions in the brainstem, OFC, and vmPFC. Animal research[3,58] has clearly shown that the ability to share and be affected by the emotional state of another is organized by basic systems subserving attachment-related processes involving the brainstem, thalamus, and paralimbic areas. The OFC and vmPFC are essential to being able to represent a particular reward or punishment level with an object and to integrating mental representations with affective value. Such interplay between basic affective mechanisms and higher order computations in the OFC plays a crucial role in the experience of empathy and feeling concern for others. Further work is necessary to elucidate the respective contribution of the lateral and medial aspects of the OFC and connectivity with brainstem nuclei in psychopathy.

Our study has several limitations. First, the tasks used here focused on passive viewing of empathy-eliciting stimuli and as such did not permit assessment of explicit cognitive and behavioral responses. These tasks were selected because they have been used extensively in neuroimaging studies with typically developing children and adults and reliably document a network involved in processing distress cues. No tasks, however, can capture the entire range of affective, cognitive, and behavioral components of what the concept of empathy emcompasses.[3-6,59] In addition, links between empathic sensitivity, as studied here, and downstream behavioral sequelae remain to be investigated in the psychopathy population. A second limitation may stem from the absence of sufficient amygdala activation in either task to allow assessment of deficits in this region in the participants with psychopathy as anticipated by the extant literature.[22,48] Bilateral amygdala activation was observed in the pooled results of the pain interactions task, but power was not sufficient to detect significant activation in the pooled pain expressions task or in any groupwise analysis. As demonstrated in a meta-analysis,[20] activity in the amygdala is frequently, but not always, detected in response to the distress or pain of others in healthy participants. Therefore, in assessing this region it may be of particular importance when working with incarcerated populations to use stimuli that are sufficiently salient, perhaps requiring the creation of materials that are more extreme in both valence and arousal than those used in typical populations.

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Online-Only Material: The eTable and eFigure are available at http://www.jamapsych.com. The Author Tables are available on request by e-mail to Dr Decety (decety@uchicago.edu).

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