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The association of prefrontal cortex response during a natural reward cue-reactivity paradigm, anhedonia, and demoralization in persons maintained on methadone

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ABSTRACT

Persons with opioid use disorder (OUD) often experience anhedonia and demoralization, yet there is relatively little research on the pathophysiology of anhedonia and demoralization in OUD treatment and recovery. In the current study, persons maintained on methadone (N = 29) underwent a natural reward-cue paradigm during functional near-infrared spectroscopy (fNIRS) imaging. Natural reward cues included highly palatable food, positive social interactions (e.g., a happy family at the dinner table), and emotional intimacy (e.g. couples embracing or kissing, but no erotic images). Participants also self-reported symptoms of anhedonia on the Snaith-Hamilton Pleasure Scale (SHPS) and demoralization on the Demoralization Scale II (DS-II). Participants who reported clinically-significant anhedonia on the SHPS displayed decreased neural activity in the right prefrontal cortex (PFC) in response to natural reward cues ($F(1,25) = 3.612$, $p = 0.027$, $\eta_p^2 = 0.302$). In linear regression models of positive social cues, decreased neural activity in the right VMPFC was associated with increased SHPS total score ($F(1,27) = 7.131$, $R^2 = 0.209$, $p = .013$), and decreased neural activity in an area encompassing the right lateral VMPFC and DLPFC was associated with increased DS-II total score ($F(1,27) = 10.641$, $R^2 = 0.283$, $p = 0.003$). This study provides initial evidence that the prefrontal cortex is involved in the pathophysiology of anhedonia and demoralization in persons in recovery from OUD. Anhedonia and demoralization are important treatment outcomes that should be queried along with a constellation of physical and mental health outcomes, to assess areas of needed improvement in methadone maintenance and other OUD treatment modalities.

1. Introduction

The United States continues to face a deadly and protracted opioid crisis that claimed over 48,000 lives in opioid-related overdose deaths in 2018 (Wilson, 2020). This unprecedented crisis has motivated the field of opioid use disorder (OUD) treatment to search for ways to enhance existing OUD treatment strategies to improve outcomes for those who are struggling to establish recovery from OUD (Bell & Strang, 2019). Maintenance on the OUD pharmacotherapy methadone remains a gold standard treatment for OUD (Volkow, Frieden, Hyde, & Cha, 2014). However, the primary goal of many methadone treatment programs is to reduce or eliminate illicit opioid use – which is highly important – but might not include interventions to improve other physical and mental health outcomes that promote healthy, sustained recovery from OUD.

There is an emerging body of literature regarding anhedonia, or an impaired capacity to experience pleasure (Snaith et al., 1995), as a key clinical feature in the progression and treatment of OUD (Destoop, Morrens, Coppens, & Dom, 2019; Kiluk, Yip, DeVito, Carroll, & Sofuoglu, 2019; Koob & Le Moal, 1997; Stevens, Peschk, & Schwarz, 2007). Previous studies have reported associations between anhedonia or low positive affect and opioid-specific treatment outcomes including increased craving and illicit drug relapse (Garfield et al., 2017; Huhn,

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Harris et al., 2016; Huhn et al., 2019). While there are relatively robust preclinical data regarding the neurobiology of devaluation of natural reward in favor of misused or illicit drugs (Carroll, Morgan, Lynch, Campbell, & Dess, 2002; Grigson & Twining, 2002; Koob & Volkow, 2010), relatively few studies have assessed the underlying pathophysiology of response to natural rewards in human models of OUD. In human laboratory studies, individuals with current heroin use have self-reported lower ratings of positively-valanced visual stimuli compared with persons who had recently achieved abstinence (De Arcos et al., 2008), and in brain imaging studies, persons with OUD displayed decreased neural activity in the left amygdala and posterior cortex (Wang et al., 2010), and in the ventromedial (VM) and dorsolateral (DL) prefrontal cortices (PFC) in response to naturally rewarding visual stimuli compared with healthy controls (Huhn, Meyer et al., 2016; Zijlstra, Veltman, Booij, van den Brink, & Franken, 2009).

These findings are consistent with a more general neurobiological model of anhedonia suggesting that responses to natural rewards are blunted as a result of decreased activity in neural reward circuits. For example, self-reported anhedonia is associated with decreased dopamine signaling from the ventral tegmental area to the nucleus accumbens and downregulation of μ opioid receptors in the nucleus accumbens, as well as decreased activity in areas associated with allocation of attention and reward processing including the rostral anterior cingulate cortex, VMPFC, and DLPFC (Der-Avakian & Markou, 2012; Park et al., 2009; Zijlstra et al., 2009). There is some evidence that self-reported anhedonia improves during protracted abstinence in opioid and other substance use disorders (Janiri, Martinotti, Dario, Reina, Paparello, Pozzi, & De Risio, 2005), yet neuroimaging studies on persons with methamphetamine use disorder suggests that even though there is some evidence of neural reregulation during protracted abstinence, decreased neural reward activity associated with anhedonia might persist for over a year (Wang et al., 2004). Moreover, there is little information available regarding anhedonia in patients on opioid maintenance therapies such as methadone, given that the majority of research on anhedonia and OUD has been in the context of post-withdrawal sequelae in abstinence-only treatment models.

Many individuals maintained on methadone might also experience feelings of demoralization, which is defined as a deprivation of spirit, courage, morale, or discipline and often conceptualized as an existential challenge (Robinson et al., 2016). Similar to anhedonia, research on the experience of demoralization in persons with OUD and specifically persons maintained on methadone is scarce. Higher levels of demoralization have been associated with more perceived psychosocial stress and greater risk for alcohol and drug use among veterans (Harling, Strehmel, Schablon, & Nienhaus, 2009), though the role of demoralization has often been lumped in with other measures of psychosocial stress (Moos, 2003). In addition, demoralization has been noted in relation to the economic burden on geographic areas or communities affected by opioid use (Mark, Woody, Juday, & Kleber, 2001). To our knowledge, the discrete pathophysiology of demoralization has not been reported. In general, demoralization and anhedonia are seen as independent constructs that are distressing to patients and may either contribute to the experience of depressive symptoms or be experienced in the context of other chronic illnesses, such as major depressive disorder or cancer (Angelino & Treisman, 2001; Clarke, Kissane, Trauer, & Smith, 2005).

Persistent anhedonia and feelings of demoralization are important yet often overlooked treatment outcomes for OUD patients, and understanding more about these constructs from a biopsychosocial perspective is imperative to developing interventions that improve OUD recovery. We previously reported that greater self-reported anhedonia and demoralization were associated with more illicit drug use in persons maintained on methadone (Huhn et al., 2019), however the biological underpinnings of anhedonia and demoralization in these individuals are not well-understood. The current study combined a natural reward cue reactivity task with functional near-infrared spectroscopy (fNIRS) imaging to examine the relationship among PFC function, anhedonia, and demoralization. We hypothesized that individuals maintained on methadone with clinically-significant levels of self-reported anhedonia would display decreased neural response to natural reward cues in the right DLPFC and VMPFC. We further hypothesized that decreased neural response to positive social cues in the VMPFC would be associated with increased self-reported anhedonia and demoralization.

2. Methods

2.1. Participants

Persons maintained on methadone were recruited from an opioid treatment program for a single study session that included an fNIRS-adapted cue reactivity task and self-reported questionnaires, and participants were tracked for 90-days post-study session to determine opioid and other drug use outcomes e.g., percent negative urine screens for opioids or any illicit drugs, which were collected as part of routine treatment; primary opioid use outcomes have been previously reported (Huhn et al., 2019). Inclusion criteria were (1) enrolled in methadone maintenance treatment for OUD, (2) aged 18 years or older, (3) right handedness, (4) passed an intoxication test at the time of their methadone dose and study session, and (5) willing to comply with study protocol. Exclusion criteria were (1) diagnosis of schizophrenia, bipolar disorder, any psychiatric condition with psychotic features, or dementia, and (2) < 3 weeks or > 18 months in methadone treatment, to exclude individuals who might be at the highest or lowest risk of relapse, and/or (3) a significant clinical problem that would compromise patient care. The Johns Hopkins Institutional Review Board approved the study protocol and all participants provided informed consent.

2.2. Assessments

The study session began directly after daily methadone dosing. Participants initially completed questionnaires concerning demographics and drug use history (McLellan, Cacciola, & Zanis, 1997), a clinical assessment of current depressive symptoms via the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), assessment of anhedonia or the inability to experience pleasure from natural rewards (score ≥ 3 indicates clinically significant anhedonia) via the Snaith-Hamilton Pleasure Scale (SHPS) (Snaith et al., 1995), and assessment of demoralization, defined as a depravation of morale or an existential challenge with independent components related to *meaning and purpose* and *distress and coping ability*, via the 16-item Demoralization Scale II (DS-II) (Robinson et al., 2016).

2.3. Natural reward cue reactivity

The fNIRS-adapted natural reward cue reactivity task was administered two hours after the participants' methadone dose, which ensured experimental control by assessing neural processing at the peak effects of methadone (Dale, Sheffels, & Kharasch, 2004; Langleben et al., 2008). Visual stimuli consisted of three categories of hedonically positive pictures (i.e. natural reward cues) – highly palatable food, positive social interactions (e.g., a happy family at the dinner table), and emotional intimacy (e.g. couples embracing or kissing, but no erotic images), as well as emotionally neutral stimuli (Bunce et al., 2015; Huhn, Meyer et al., 2016). Natural reward and neutral images were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1997). Images were presented on a 16-inch monitor (75 Hz refresh rate) using E-Prime software (Psychology Software Tools Inc., PA). Positive reward stimuli were presented in 25 s blocks comprised of 5 pictures from a single category (e.g. positive social, neutral), each displayed for 5 s. The order of images within blocks and the order of blocks within the experiment were randomized for each individual. A black screen with a crosshair in the center was shown for 15 s between blocks to allow

hemodynamic response to return to baseline.

2.4. Functional Near-infrared spectroscopy measurement and processing

fNIRS measures regional changes in cerebral blood flow (an indirect measure of neural activity) by detecting infrared light spectra for oxygenated and deoxygenated hemoglobin (Ferrari & Quaresima, 2012; Villringer & Chance, 1997). Data were recorded using a continuous wave system (fNIR1200, fNIR Devices, LLC, USA) and a 4 × 10 (4 LED light sources and 10 photodetectors) optode set yielding 16 channels (Ayaz et al., 2011). Hemodynamic response was recorded using COBI Studio during each 25-second block (positive and neutral). Sensors were located by aligning the bottom row of optodes with the International 10–20 sites F7, FP1, FP2, F8 line (Ayaz et al., 2012; Jasoer, 1958). This placement situated the sensor over bilateral VMPFC (Brodmann Area 10) and VL/DLPFC (Ayaz et al., 2006; Okamoto et al., 2004).

fNIRS data processing used raw light intensity from 16 optodes with two wavelengths that were low-pass filtered with a finite impulse response, with a linear phase filter with order 20 and a cut-off frequency of 0.1 Hz (to attenuate high frequency noise, respiration, and cardiac cycle effects). All data were inspected for potential saturation and motion artifact contamination by means of a coefficient of variation-based assessment (Ayaz, Izzetoglu, Shewokis, & Onaral, 2010) and were corrected for motion artifacts. The final output of each optode was change from baseline oxygenated hemoglobin (HbO_2) during 25 sec blocks of time when participants were viewing positive natural rewards or neutral visual stimuli. For each participant, a mean change from baseline HbO_2 was calculated for each positive or neutral condition in each of the 16 optodes, then the neutral condition was subtracted from the positive condition to control for attending to visual stimuli. Increased or decreased HbO_2 was treated as a secondary marker of increased or decreased neural activity, respectively.

2.5. Statistical analyses

Demographic and drug use characteristics were compared between participants who did versus did not endorse clinically-significant anhedonia (evidenced by a score of ≥ 3 on the SHPS) via Independent-sample t-tests or chi-squared analyses, as appropriate. Group differences in response to positive natural rewards was assessed using analysis of covariance (ANCOVA) for participants who did or did not endorse clinically-significant anhedonia; while there were no significant differences in demographic or drug use characteristics, this analysis controlled for days in treatment and methadone dose because group differences in those variables may have been clinically-meaningful (Table 1). Linear regression was then used to examine the association between neural activity while viewing positive natural rewards and outcomes including the HAM-D, SHPS, and DS-II total scores, as well as percent opioid-negative and/or all illicit drug-negative urine screens during the 90-day follow-up. Urine drug screens were collected by the treatment center at daily methadone dosing, and thus missed urine screens would correspond to missed methadone doses and relapse. As an exploratory analysis, linear regression was also utilized to examine the association between viewing positive social stimuli and the aforementioned outcomes. Given that results were significant, a hierarchical regression model was conducted, controlling for days in treatment and methadone dose in the first block, and SHPS or DS-II results in the second block. Results were reported as change in F or R^2. For all fNIRS analysis, ≥ 3 adjacent optodes had to be independently significant at $p < .05$ via independent-samples t-tests or linear regression before optodes were clustered for final analyses. All other analyses were considered significant at $p < .05$. Statistical analyses were performed in SPSS version 25 (IBM, Armonk, NY).

Table 1
Participant Characteristics.

	Did Not Endorse Anhedonia (n = 20)	Clinically Significant Anhedonia (n = 9)	t or χ2 (p-value)
Age in years M (SD)	42.1 (13.2)	42.0 (14.9)	0.18 (0.986)
Sex (% Male)	55.0	66.7	0.35 (0.555)
Race (% White)	80.0	100	2.01 (0.148)
Ethnicity (% Hispanic)	5.0	0	0.47 (0.495)
Years Education M (SD)	12.9 (2.9)	11.6 (2.4)	1.16 (0.256)
Living Situation (% Homeless)	10.0	0	0.97 (0.326)
Methadone Dose mg M (SD)	73.2 (22.6)	81.5 (24.1)	−0.89 (0.399)
Days in Treatment M (SD)	159.3 (181.1)	231.6 (191.7)	−0.98 (0.337)
Past 30-day Drug Use at Baseline			
Heroin Days M (SD)	2.2 (6.7)	4.0 (7.2)	−0.66 (0.518)
Opioid Days M (SD)	0.6 (1.7)	0.8 (2.3)	−0.30 (0.766)
Cocaine Days M (SD)	6.4 (11.4)	3.4 (6.6)	0.87 (0.395)
Alcohol Days M (SD)	0.8 (2.4)	0.4 (1.3)	0.41 (0.687)
Marijuana Days M (SD)	3.9 (9.5)	1.3 (3.3)	0.76 (0.452)
Benzodiazepine Days M (SD)	0.4 (0.9)	0.3 (1.0)	0.04 (0.966)
Lifetime Years of Heroin Use M (SD)	5.9 (7.5)	7.1 (9.3)	−0.37 (0.711)
Lifetime Years of Rx Opioid Use M (SD)	6.3 (6.5)	7.6 (8.5)	−0.48 (0.634)
Lifetime Years of Cocaine Use M (SD)	3.6 (6.3)	3.6 (3.8)	0.18 (0.986)
Lifetime Diagnosis Depression (%)	35.0	33.3	0.01 (0.930)
CNS-active Medications (%)			
SSRI	20.0	11.1	0.34 (0.558)
Trazodone	25.0	11.1	0.73 (0.393)
Gabapentin	15.0	11.1	0.08 (0.779)

M = mean, SD = standard deviation, RX = prescription, SSRI = selective serotonin reuptake inhibitor, SARI = serotonin antagonist and reuptake inhibitor.

3. Results

Thirty individuals maintained on methadone were recruited into this study and one was excluded for excessive head movement during fNIRS imaging, resulting in a final N = 29. Regarding drug use outcomes, 12/29 participants tested positive for opioids during the 90-day follow-up and these individuals provided a mean (SD) 41.5% (28.6) opioid-positive urine drug screens; 17/29 participants tested positive for any illicit drug, including opioids, cocaine, marijuana, and/or benzodiazepines during follow-up and these individuals provided a mean (SD) 83.0% (26.1) illicit drug-positive urine screens. Participants who did (n = 9) versus did not (n = 20) endorse clinically significant anhedonia on the SHPS were similar in mean (SD) age [42.0(14.9) years vs 42.1(13.2) years], sex (66.7% vs 55.0% male), and race (80% vs 100% white). No significant differences in demographics or drug use history were observed (Table 1). In addition, participants who did versus did not endorse clinically significant anhedonia did not differ in HAM-D scores [11.44(9.03) vs 9.70(8.30); t(27) = −0.51, p = .614], and displayed marginally greater DS-II total scores [12.78(9.99) vs 7.30(6.64); t(27) =

−1.75, p = .091].

Participants who did versus did not endorse clinically-significant anhedonia displayed decreased neural activity in the right PFC in response to natural reward cues when controlling for days in treatment and methadone dose ($F(1, 25) = 3.612$, $p = 0.027$, $\eta_p^2 = 0.302$; Fig. 1). In linear regression models of positive social cues, decreased neural activity in the right VMPFC was associated with increased SHPS total score ($F(1,27) = 7.131$, $R^2 = 0.209$, $p = .013$), and decreased neural activity in an area encompassing the right lateral VMPFC and DLPFC was associated with increased DS-II total score ($F(1,27) = 10.641$, $R^2 = 0.283$, $p = 0.003$; Fig. 1). In a hierarchical regression model of positive social cues that controlled for days in treatment and methadone dose, decreased neural activity in the right VMPFC was marginally associated with increased SHPS total score ($\Delta F(1,25) = 3.98$, $\Delta R^2 = 0.098$, $p = 0.057$), and decreased neural activity in an area encompassing the right lateral VMPFC and DLPFC was associated with increased DS-II total score ($\Delta F(1, 25) = 10.604$, $\Delta R^2 = 0.278$, $p = 0.003$). Decreased PFC activity during the natural reward-cue paradigm was not associated with HAM-D total score or opioid use during the 90-day follow-up based on *a priori* criteria that ≥ 3 adjacent optodes were independently significant at $p < .05$. Decreased PFC activity in response to social cues was observed in two optodes in the VLPFC (optodes 12 and 14 – see Fig. 1 for reference) that were associated with any illicit substance use during the 90-day follow-up ($t(27) = 2.055$, $p = .05$), but since this activity was not significant in ≥ 3 adjacent optodes, it was not considered significant for the purpose of this study.

4. Discussion

This study provides initial evidence that the prefrontal cortex is involved in the pathophysiology of anhedonia and demoralization in persons in recovery from OUD. More specifically, the results of this study demonstrated that persons maintained on methadone who self-reported clinically-significant levels of anhedonia display decreased neural activity in the right PFC when compared with methadone patients who did not report clinically significant anhedonia (Fig. 1). Moreover, study results demonstrated that decreased neural activity in the right VMPFC and an area encompassing the right lateral VMPFC and DLPFC while viewing positive social stimuli was associated with symptoms of anhedonia and demoralization, respectively. Previous neuroimaging studies in persons with OUD who were abstinent from opioids have also found decreased neural activity in the VM/DLPFC in response to naturally rewarding visual stimuli (Huhn, Meyer et al., 2016; Zijlstra et al., 2009), and there is some evidence that anhedonia is related to reduced neural activity in brain reward pathways during protracted abstinence from methamphetamine use (Wang et al., 2004), although longitudinal neuroimaging studies are necessary to better understand the course and consequence of anhedonia and brain function in OUD patients. While neuroimaging results were not significantly associated with opioid use during the 90-day follow-up in this study, it is possible that this study was under-powered to detect a significant relationship. Decreased response to social cues in a small portion of the right VLPFC was associated with any illicit drug use during follow-up, but these results did not meet our *a priori* criteria for inclusion; studies with larger samples, use of other natural reward stimuli such as individualized scripts (Seo et al., 2013), or studies that use fMRI to examine functional connectivity during natural reward-cue paradigms might further elucidate the relationship among brain response, anhedonia, demoralization, and continued illicit drug use.

It is noteworthy that anhedonia and demoralization may be deeply troubling to patients and are important treatment outcomes, independent of relapse, that should be the target of interventions for persons maintained on methadone. In a previous study with this patient sample, we demonstrated that self-report measures of anhedonia and demoralization were associated with opioid and any illicit drug use during the 90-day follow-up (Huhn et al., 2019). Nonetheless, emphasizing outcomes other than opioid use is consistent with broader changes in the field of OUD treatment, which is increasingly recognizing the need to develop comprehensive treatments that address a wider array of patient physical and mental health problems (Hsu, Marsteller, Kachur, & Fingerhood, 2019; Mahoney, Reich, & Urbanek, 2019). Elucidating the underlying pathophysiology of anhedonia and demoralization in this population could lead to novel treatment approaches to improve quality of life in recovery. Potential treatments include transcranial magnetic or direct current stimulation, cognitive behavioral therapy, and/or pharmacological interventions that improve depressive symptoms (Dunn, Huhn, Bergeria, Gipson, & Weerts, 2019; Lalanne et al., 2017; McHugh, Hearon, & Otto, 2010; Nakamura-Palacios et al., 2016; Salling & Martinez, 2016; Spano et al., 2019). Brain stimulation techniques may be particularly relevant in treating OUD and anhedonia, as a study using continuous theta burst stimulation of the VMPFC demonstrated reduced drug and alcohol cue-reactivity (Kearney-Ramos et al., 2018), and a study using repeated transcranial magnetic stimulation in persons with cocaine use disorder demonstrated improvements in craving scores and depressive symptoms, including anhedonia, after 4 weeks of treatment (Pettorruso et al., 2019).

Anhedonia was prevalent in this sample, evidenced by the fact that nearly one-third of participants endorsed clinically-significant anhedonia on the SHPS (Table 1). Participants who did versus did not endorse clinically-significant anhedonia did not report significantly greater depressive symptoms via the HAM-D; while anhedonia is a symptom of major depressive disorder (Treadway & Zald, 2011), it is also an independent construct that might reflect abnormal hedonic tone or persistently low positive affect (Rizvi, Pizzagalli, Sproule, & Kennedy, 2016; Treadway & Zald, 2011), regardless of other depressive symptoms. Participants who did versus did not endorse clinically-significant anhedonia also reported marginally higher scores on the DS-II, suggesting greater levels of demoralization. These results did not reach the level of statistical significance but may still be clinically-meaningful. We previously reported that anhedonia and demoralization shared 29.2% variance with one another in this patient sample, suggesting that these clinical phenomenon are related to each other in OUD recovery (Huhn et al., 2019). Still, anhedonia and demoralization are – by definition – separate constructs that might independently or concurrently be distressing to persons in OUD recovery. There is almost no research on demoralization in OUD, yet the real-world experience of many persons with OUD suggests that demoralization is present within this patient population and that it may serve as a barrier to persons initiating treatment and achieving sustained recovery. More research is needed to better understand how low positive affect, high negative affect, and psychosocial stress might contribute to feelings of demoralization, as well as the role of demoralization in self-defeating behaviors that are often expressed in persons with OUD (Goldstein & Volkow, 2011).

This study is limited by a small sample size, although the sample in this study is similar to other neuroimaging studies of persons with OUD (Wang et al., 2010, 2011; Zijlstra et al., 2009). This study is also limited by the lack of racial/ethnic diversity of participants. Although fNIRS does not provide an assessment of neural activity in sub-cortical brain regions, it has several strengths for use in clinical settings. These include its portability and ease of use relative to fMRI, which would facilitate its deployment in clinical settings to assess the trajectory of healthy recovery from OUD, including improvements in PFC response to natural rewards. Finally, this study provided valuable cross-sectional evidence of a positive signal and future research could utilize a repeated measures design with fNIRS to examine possible improvements in both neural function and self-reported anhedonia or demoralization.

5. Conclusion

In conclusion, this study provides initial evidence that PFC response to natural rewards could be used as a biological marker of anhedonia and demoralization in persons receiving methadone for the treatment of

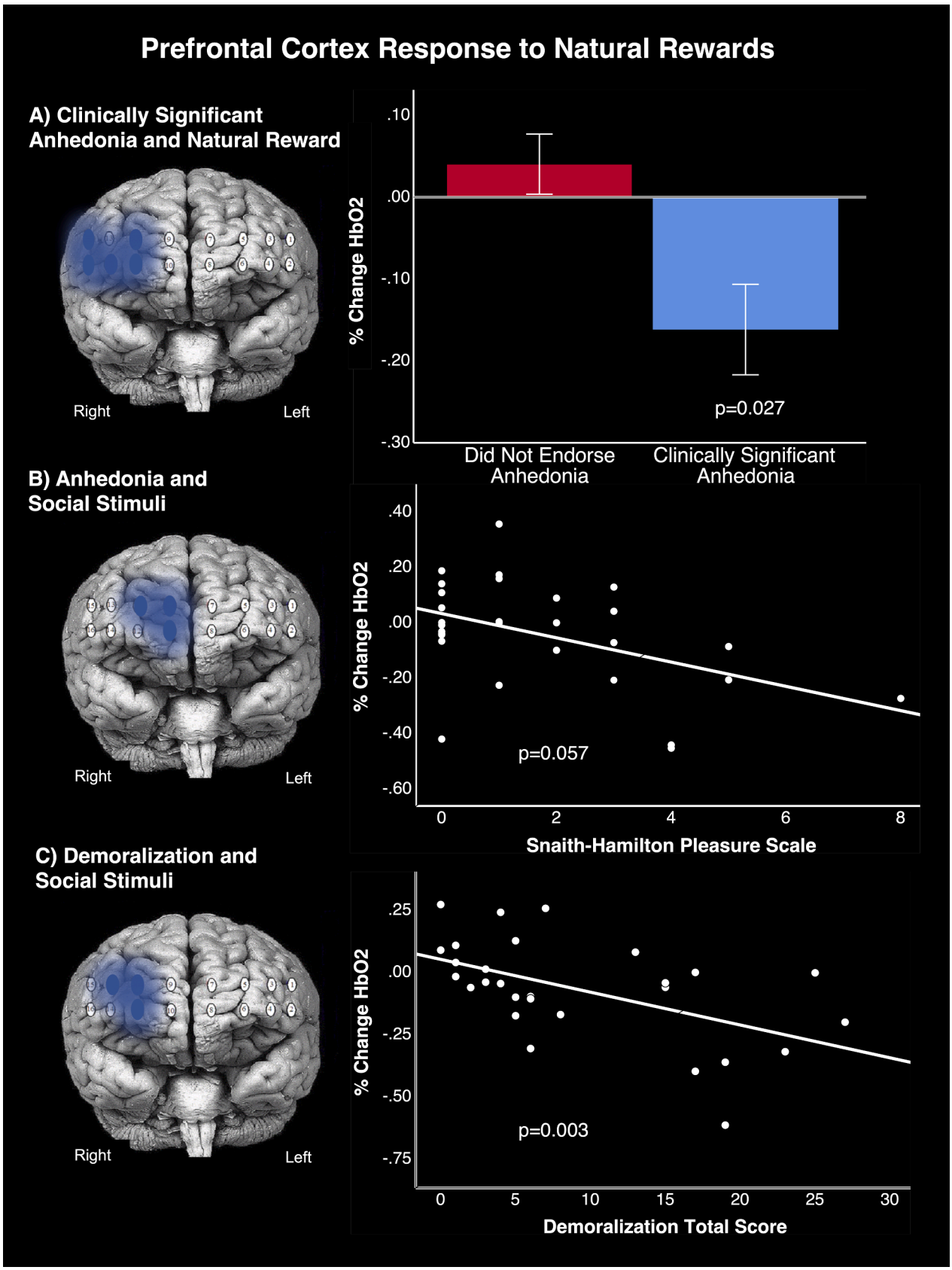

Fig. 1. Functional near-infrared spectroscopy (fNIRS) results from a natural reward cue reactivity task. All analyses represent baseline-corrected change in oxygenated hemoglobin in response to natural reward minus neutral cues, controlling for days in treatment and methadone dose. A) Group differences between methadone patients that did or did not endorse clinically-significant anhedonia on the Snaith-Hamilton Pleasure Scale (SHPS). Results represent all natural reward categories (food, social, and intimate stimuli). B) Regression analysis of response to positive social stimuli and SHPS. C) Regression analysis of response to positive social stimuli and the Demoralization II scale.

OUD. This study demonstrated that decreased PFC activity in response to natural rewards - and specifically positive social interactions – was associated with increased self-reported anhedonia and demoralization. Anhedonia and demoralization are, in and of themselves, distressing to patients. These data support additional research to further evaluate the prevalence, consequences, and correlates of anhedonia and demoralization in persons with OUD, and suggests that these domains should be queried along with a constellation of physical and mental health outcomes, to assess areas of needed improvement in methadone maintenance and other OUD treatment modalities.

6. Contributors

AH, RB, and KD designed the study. All authors contributed to manuscript preparation and revision of the manuscript. AH and HA are responsible for data processing and data analyses.

CRediT authorship contribution statement

Andrew S. Huhn: Conceptualization, Funding acquisition, Supervision, Investigation, Writing - review & editing, Formal analysis, Validation, Visualization, Data curation, Investigation, Methodology. **Robert K. Brooner:** Conceptualization, Funding acquisition, Supervision, Investigation, Writing - review & editing. **Mary M. Sweeney:** Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Denis Antoine:** Writing - original draft, Writing - review & editing. **Alexis S. Hammond:** Writing - original draft, Writing - review & editing. **Hasan Ayaz:** Formal analysis, Validation, Visualization. **Kelly E. Dunn:** Conceptualization, Funding acquisition, Supervision, Investigation, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HA was involved in the technology development of the brain-imaging instrument manufactured by fNIR Devices, LLC and owns a minor share of the firm. fNIR Devices, LLC manufactures the optical brain imaging instrument and licensed IP and know-how from Drexel University. ASH receives research funding from Ashley Addiction Treatment through his university. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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