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Research report

Evidence of anhedonia and differential reward processing in prefrontal cortex among post-withdrawal patients with prescription opiate dependence

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ABSTRACT

Anhedonia is an important but understudied element of a neuroadaptive model underlying vulnerability to relapse in opioid dependence. Previous research using fMRI has shown reduced activation to pleasant stimuli in rostral prefrontal cortex among heroin-dependent patients in early recovery. This study evaluated the presence of anhedonia among recently withdrawn prescription opiate dependent patients (PODP) in residential treatment compared to control subjects. Anhedonia was assessed using self-report, affect-modulated startle response (AMSR), and a cue reactivity task during which participant's rostral prefrontal cortex (RPFC) and ventrolateral prefrontal cortex (VLPFC) was monitored with functional near infrared spectroscopy (fNIRS). The cue reactivity task included three distinct categories of natural reward stimuli: highly palatable food, positive social situations, and intimate (non-erotic) interactions. PODP reported greater anhedonia on self-report (Snaith–Hamilton Pleasure Scale), and showed reduced hedonic response to positive stimuli in the AMSR task relative to controls. PODP also exhibited reduced neural activation in bilateral RPFC and left VLPFC in response to food images and reduced left VLPFC in response to images depicting positive social situations relative to controls. No differences were found for emotionally intimate stimuli. When patients were divided into groups based on the Snaith–Hamilton criteria for the presence or absence of anhedonia, patients endorsing anhedonia showed reduced neural responses to images depicting positive social stimuli and food relative to patients who did not endorse anhedonia. Activations were in areas of RPFC that support the retrieval of episodic memories. The results suggest the presence of anhedonia in a subsample of PODP.

1. Introduction

The prevalence of prescription opioid dependence in the United States has increased considerably in the past two decades (Johnston et al., 2011; Substance Abuse and Mental Health Services Administration, 2013). According to the Centers for Disease Control and Prevention, the annual quantity of painkillers prescribed in the United States has quadrupled since the turn of the century, despite the absence of an increase in reported pain (Substance Abuse and Mental Health Services Administration, 2013). Prescription opiates have also become a gateway drug to the use of heroin, as prescription drugs have become harder to abuse, less available, and more expensive to buy on the street (Muhuri et al., 2013). Addiction has been characterized as a chronic relapsing disorder, and, as with other chronic medical disorders, addressing factors that affect the risk of recurrence/relapse is essential to successful patient care (O'Brien et al., 1998; Tkacz et al., 2012).

There is growing evidence that anhedonia, defined as an impaired capacity to experience pleasure (Snaith, 1993), plays an important role in vulnerability to relapse across addictive disorders (Franken et al., 2007; Garfield et al., 2014; Janiri et al., 2005; Koob and Le Moal, 2001; Volkow et al., 2002).

Abbreviations: (PODP), Prescription opiate dependent patients; (AMSR), ffect-modulated startle response; (PFC), prefrontal cortex; (RPFC), rostral PFC; (VLPFC), ventrolateral PFC; (fNIRS), functional near-infrared spectroscopy.

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Anhedonia has been found to be a common symptom of the abstinence syndrome associated with both acute and protracted withdrawal in substance-dependent populations (Bovasso, 2001; Gawin and Ellinwood, 1988; Garfield et al., 2014; Hatzigiakoumis et al., 2011; Heinz et al., 1994; Leventhal et al., 2009, 2010; Loas, 1996; Martinotti 2008b), including opiate-dependence (Martin et al., 1963; Martin et al., 1973; Zijlstra et al., 2009). Emotional disturbances, including anhedonia, have been thought to contribute to the high rates of relapse (Alling et al., 1982; Begleiter and Porjesz, 1979; Martin et al., 1963, 1973). Research in animal models, summarized by Koob and Le Moal (2001), provides support for an allostatic model of addiction, in which the natural homeostatic mechanisms of the hypothalamic/pituitary/adrenal (HPA) axis and brain reward system are altered over the course of chronic drug self-administration. As a consequence of these adaptations, new set points are established, leaving the addicted individual more susceptible to stress, less responsive to natural rewards, and more responsive to drug cues. These allostatic changes persist following drug withdrawal, and are believed to contribute substantially to risk of relapse (Koob and Kreek, 2007; Koob and Volkow, 2010). Anhedonia has also been posited to play a role in the onset of addiction (Blum et al., 2000). The reward deficiency syndrome hypothesis posits that genetically-conferred deficits in hedonic capacity, particularly hypodopaminergic activity in meso-limbic dopaminergic centers, lowers the capacity to cope with stress, and increases the risk of seeking pharmacological reinforcers. This inherent form of anhedonia would not only place the individual at increased risk for developing an addiction, but would also make them more vulnerable to relapse as they attempted to maintain their abstinence in recovery. These two theories suggest potentially overlapping mechanisms by which anhedonia may confer risk in recovery from substance use disorders.

Whereas clinical phenomena such as craving, tolerance, withdrawal and enhanced response to drug cues have been studied in recovering opioid dependent patients (e.g., Koob and Volkow, 2010; Kühn and Gallinat, 2011; Lubman et al., 2009; Zijlstra et al., 2009), relatively few studies have evaluated the role of reduced responses to natural rewards in these clinical populations. This is notable, given the potential role of anhedonia in explaining vulnerability to relapse and the supporting evidence from preclinical models (e.g., Grigson and Twining, 2002; Koob and Volkow, 2010; Markou and Koob, 1991). In addition to anhedonic mood, behavioral measures have validated reduced ratings of pleasant stimuli among current and abstinent heroin users (de Arcos et al., 2008). Anhedonia has been associated with greater drug craving among recently withdrawn opioid-dependent (Janiri et al., 2005; Martinotti et al., 2008a) and alcoholic patients (Martinotti et al., 2008a,b). Tobacco smokers attempting to quit are more likely to relapse if they are anhedonic (Cook et al., 2010; Leventhal et al., 2009; Versace et al., 2011). A recent review of the literature suggests that the explanatory role of anhedonia in substance use disorders cannot be accounted for simply as a factor of comorbidity with other psychiatric diagnoses in which anhedonia is common (e.g., depression; Garfield et al., 2014). These findings suggest anhedonia warrants investigation as an independent construct.

Studies using functional magnetic resonance imaging (fMRI) in conjunction with affectively positive stimuli have reported relatively less neural activity in limbic (right amygdala; Wang et al., 2010), as well as posterior cortical (Wang et al., 2010) and anterior cortical locations (Zijlstra et al., 2009) in abstinent heroin dependent patients relative to controls. Of particular relevance to the current study, Zijlstra et al. (2009) used fMRI to evaluate neural responses to positive hedonic stimuli and drug cues among recently detoxified heroin-dependent males. They found that the pleasant cues activated bilateral dorsolateral prefrontal cortex (PFC), ventrolateral PFC, and anterior prefrontal gyrus (or rostral prefrontal cortex; RPFC) in both opioid-dependent and control participants. Patients differed from controls only in the bilateral rostral (i.e., anterior) PFC, where heroin-dependent participants showed reduced neural activation relative to controls. Whereas the data offered by Zijlstra et al. (2009) appear to be relevant to the construct of anhedonia, they did not find group differences on a well-validated self-report measure of anhedonia; the Snaith–Hamilton Pleasure Scale (SHAPS; Franken and Muris, 2006; Snaith et al., 1995).

Although prior neuroimaging studies of cued responses in patients with substance use disorders have relied heavily on functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), the real-world clinical application of these technologies is limited by the expense and the reality that the vast majority of addiction treatment programs exist apart from functional brain imaging centers. The current study is part of a larger effort to develop objective CNS measures that have clinical relevance and potential utility in the assessment of patients recently withdrawn from opioids. Functional near-infrared spectroscopy (fNIRS) of the frontopolar, dorsolateral, and ventrolateral PFC is one such technology. There are several advantages to using fNIRS, including cost, ease of use, portability, and clinical relevance (Bunce et al., 2012; Irani et al., 2007; Ehlis et al., 2014). In particular, this technology holds promise for the assessment of cortical activity in response to drug cues and natural reward stimuli. The PFC plays a major role in several addiction-related neural functions, including decision making (Fu et al., 2008; Gilbert et al., 2006), impulsivity (Rao et al., 2008), self-control (Brody et al., 2007), emotional regulation (Kringelbach and Rolls, 2004; Wang et al., 2010), and motivation and salience attribution (Ventura et al., 2007). Whereas there is increasing evidence that the PFC makes an important contribution to the cycle of addiction (Goldstein and Volkow, 2011), the role of PFC function post-withdrawal as it relates to relapse, or risk of relapse, remains unclear.

In a recent cross-sectional study of patients in residential treatment for prescription opioid-dependence, Bunce et al. (2015) used fNIRS, coupled with a cued response task, to evaluate PFC responses of extended care patients who had been abstinent for an average of 79 days ($n = 7$) relative to recently withdrawn patients ($n = 7$) abstinent for an average of 19 days, and healthy controls ($n = 7$). The results suggested that the two patient groups differed in their PFC responses to natural reward cues as well as to drug cues, whereas the responses of the extended care patients did not differ from those of the controls. Similar results have also been demonstrated in an alcohol-dependent population (Bunce et al., 2012) using fNIRS.

The purpose of the current study was to use a multimodal approach to evaluate the presence of anhedonia among recently withdrawn prescription opiate dependent patients (PODP) compared with control participants, including: 1) a well-validated self-report measure of anhedonia, the SHAPS (Snaith et al., 1995); 2) a well-validated psychophysiological measure of hedonic evaluation, the affect modulated acoustic startle response (AMSR; Bradley et al., 1999; Lang, 1995); and 3) a cue response task to images of naturally rewarding stimuli while participants were monitored over bilateral rostral (RPFC) and ventrolateral prefrontal cortices (VLPFC) with fNIRS. We expected patients to report greater levels of anhedonia on the SHAPS (although not all studies have found patient-control differences, e.g., Zijlstra et al., 2009). The AMSR provides an objective measure of stimulus evaluation that is not subject to the biases of self-report. We also expected patients to show increased startle amplitude while viewing the positive images in the AMSR paradigm relative to controls, a response that is indicative of a less positive evaluation.

To increase our understanding about the specificity of response to natural reward cues in PODP, participants viewed images of three distinct types of natural rewards: highly palatable food, positive

Table 1
Participant demographic characteristics: recently withdrawn patients versus healthy controls.

	PODP	Healthy controls
N	36	10
% Female	25%	40%
Mean age (SD)	28.8 (9.7)	25.1 (2.5)
% Past major depression	20%	0%
% History of depression	29%	20%
% GAD	38%	0%
% History of anxiety	20%	10%

social situations, and intimate interactions. Based on prior research, we hypothesized that these three categories of natural rewards would elicit reduced neural activity in anhedonic patients, relative to controls, in bilateral anterior prefrontal gyrus, also referred to as lateral RPFC, and VLPFC (Zijlstra et al., 2009). Finally, using the criteria established by Snaith et al. (1995) for identifying a clinical level of anhedonia, we hypothesized that patients who endorsed self-reported anhedonia, relative to patients who did not endorse anhedonia, would show reduced neural responses to images of natural rewards in these RPFC areas.

2. Methods

2.1. Participants

Patients ($n = 36$) were recruited from the Caron Treatment Center, a residential treatment facility in Wernersville, Pennsylvania (see Table 1). PODP participants were recruited 10–14 days after they had completed medically assisted withdrawal at Caron, with data acquisition occurring 18–25 days after entry into the treatment center. The study was approved by the Penn State Hershey Medical Center IRB, and all participants signed IRB-approved consent forms after a full explanation of procedures, and prior to their engagement in any study procedures. Patient inclusion criteria included: (1) capable and willing to comply with the research protocol; (2) met criteria for opioid dependence {Diagnostic and Statistical Manual for Mental Health Disorders – Fourth Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), as determined by clinical staff at the Caron Foundation, and the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002), and Form-90D (Westerberg et al., 1998)}; (3) prescription opioids were the primary drug of choice; (4) over the age of 18; (5) staying in residential treatment for at least 30 days; (6) right handedness. Exclusion criteria included (1) any history of Bipolar I disorder, cyclothymia, schizophrenia or psychosis, as diagnosed by the SCID; (2) current major depressive disorders; 3) intravenous drug use; 4) history of traumatic brain injury; (5) current use of any opiate agonist (methadone or buprenorphine) or antagonist (Naltrexone). Current dysthymia was allowed in the study. Healthy controls ($n = 10$) were recruited at the Hershey Medical Center in Hershey, Pennsylvania. Control participants, matched for age and gender, had no history of drug or alcohol abuse or dependence, and no current DSM-IV-TR Axis I disorders (as determined by the SCID and Form-90D).

2.2. Data collection

2.2.1. Procedure

Participants were scheduled for laboratory session approximately 2 h after their last meal. At the outset of the laboratory session, participants completed the Snaith–Hamilton Pleasure Scale (SHAPS), followed by a cue reactivity task and an affect modulated startle response task. During the cue reactivity task, participants were monitored with fNIRS over bilateral rostral prefrontal cortex (Brodmann Area 10) and ventrolateral prefrontal cortex (Brodmann Areas 46/47).

2.2.2. The Snaith–Hamilton Pleasure Scale

The Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995) is a 14-item questionnaire designed to assess the relative capacity or incapacity to experience pleasure hedonic tone, or, conversely, anhedonia. Each item (e.g., "I would enjoy seeing other people's smiling faces") is rated on a 4-point Likert scale, labeled *Strongly disagree*, *Disagree*, *Agree*, or *Strongly agree*. With a total score of 0–14, higher total scores on the SHAPS indicate higher levels of anhedonia. A cutoff score of 2 was established to identify which participants could be labeled as anhedonic (Franken et al., 2007; Snaith et al., 1995). The SHAPS was designed to keep gender, age, and cultural biases to a minimum and the items refer to common experiences that are likely to be encountered by most people (Snaith et al., 1995). The scale has been shown to be highly reliable, with good internal consistency and test–retest reliability in both community and patient samples (Franken et al., 2007). It has also been demonstrated to correlate with related measures of affect and personality in a theoretically meaningful way. Patients with substance dependence, depression, and psychosis have been found to have higher scores on the SHAPS than non-patient controls (Franken et al., 2007). Convergent validity derives from correlations with the Hedonic Tone item on the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), the Anhedonic Depression subscale on the Mood and Anxiety Symptom Questionnaire, and the Positive Affect subscale from the Positive and Negative Affect Schedule (Franken et al., 2007; Gilbert et al., 2002; Snaith et al., 1995). Its discriminant validity has been supported by its lack of association with MADRS Depressed Mood and Anxiety items (Franken et al., 2007; Snaith et al., 1995).

2.2.3. Affect-modulated acoustic startle response

Affect-modulated acoustic startle response (AMSR), a well-known psychophysiological measure of emotional valence (Lang 1995; Bradley et al., 1999), was used to assess hedonic responses to standardized reward-related stimuli. Participants viewed 12 pictures in each of four categories. Three categories, emotionally positive, negative, and neutral stimuli, were drawn from the International Affective Picture System (IAPS; Lang et al., 2008). Stimuli for the fourth category, drug-related images, were created by authors AH & SB (responses to be reported in a separate paper). Stimulus order was randomized for each individual, and no stimuli were shared with the cued-reactivity task. The acoustic startle probe, a 50-ms burst of 104 dB white noise with instantaneous rise time, was presented at variable points during the 6-second slide viewing period, ranging from 3.5 to 5.5 s after slide onset. The probe was presented on 9 of the 12 slides for each type, and four startle probes were presented in the intervals between picture presentations to minimize predictability. Startle probes were presented binaurally through stereo headphones with presentation and timing of stimuli controlled by E-Prime software (Psychology Software Tools Inc., PA). The eye-blink component of the startle reflex was measured by recording electromyographic (EMG) activity from 4-mm Beckman miniature Ag/AgCl electrodes positioned over the orbicularis oculi muscle beneath the left eye. Startle responses were standardized within participants; *Z* scores for each participant were compared by condition (positive, negative, neutral). Two PODP and one control were non-responders (i.e., no reliable startle response was detected), and were excluded from further analysis, and one PODP patient was excluded due to technical difficulties.

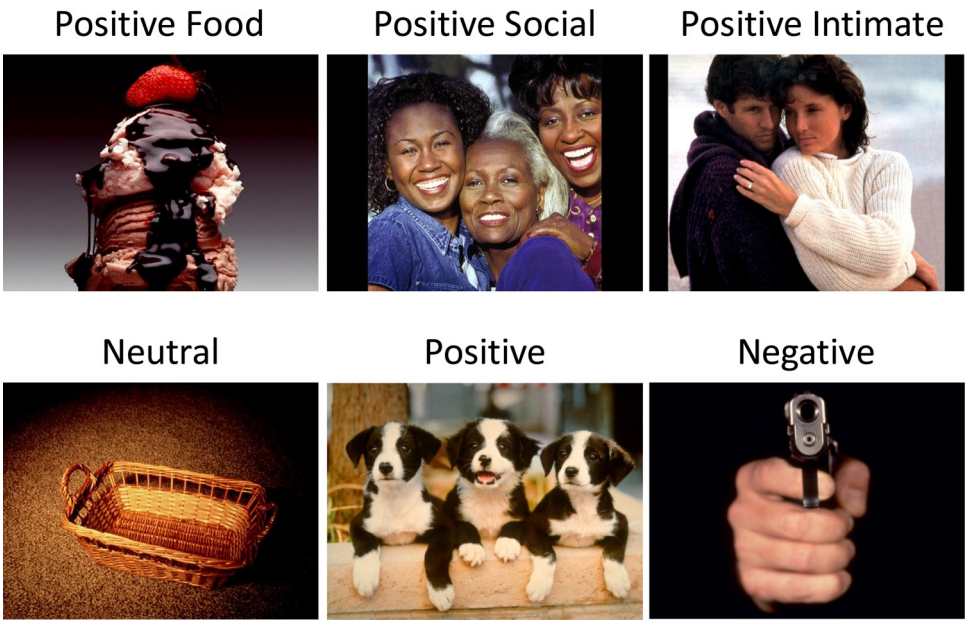

Fig. 1. Examples of visual stimuli presented to recently withdrawn patients and controls during cue response paradigm for functional near infrared spectroscopy (fNIRS) and affect-modulate acoustic startle response (AMSR). Top row displays three types of positive natural rewards (highly palatable food, positive social situation, and intimate interaction) used in the fNIRS task. Bottom row shows positive and negative affective stimuli used in the ASAM task. Both tasks displayed neutral stimuli.

2.2.4. Cue reactivity task with fNIRS monitoring

All participants completed a standard visual cue reactivity paradigm while being monitored with fNIRS. Stimuli (see Fig. 1) consisted of three categories of hedonically positive stimuli – highly palatable food, positive social interactions (e.g., a happy family at the dinner table), and emotional intimacy (couples embracing or kissing, but no erotic images), as well as emotionally neutral stimuli. Natural reward and neutral images were selected from the IAPS (Lang et al., 2008). Images were presented on a 16 in monitor (75 Hz refresh rate) using E-Prime software (Psychology Software Tools Inc., PA). Stimuli were presented in 25 s blocks comprised of 5 pictures from a single category, 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 10 s between blocks.

Functional near-infrared spectroscopy measures regional changes in cerebral blood flow (an indirect measure of neural activity) by detecting infrared light spectra for oxygenated and deoxygenated hemoglobin (e.g., Villringer and Chance, 1997; for recent reviews see Ferrari and Quaresima, 2012; Scholkmann et al., 2014). In the current study, data were recorded using a continuous wave system (fNIR1100, fNIR Devices, LLC, USA) and a 4×10 (4 LED light sources and 10 photodetectors) optode set yielding 16 channels. Sensors were located by aligning the bottom row of optodes with the International 10–20 sites F7, FP1, FP2, F8 line (Jasper, 1958). This placement situated the sensor over bilateral rostral prefrontal cortex (Brodmann Area 10) and ventrolateral prefrontal cortex (Okamoto et al., 2004).

2.2.5. fNIRS signal processing

fNIR data were processed using a software suite developed at Drexel University and implemented in Matlab (The Mathworks, Inc., Sherborn, MA). Raw light intensity data from the 16 optodes and two wavelengths were low-pass filtered with a finite impulse response, 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 (Ayaz et al., 2011). All data were inspected for potential saturation (when light intensity at the detector is higher than the analog-to-digital converter limit) and motion artifact contamination by means of a coefficient of variation based assessment (Ayaz et al., 2010). The data for each task block were extracted and hemodynamic changes for each of the 16 optodes were calculated separately for each block using the Modified Beer Lambert Law. The final output of each optode was mean deoxygenated hemoglobin (HbR), mean oxygenated hemoglobin (HbO_2), and mean total hemoglobin (Total Hb) calculated for each stimulus type, palatable food, positive social interactions, and emotional intimacy, and hedonically neutral stimuli. Analyses were calculated using mean HbO_2.

2.3. Statistical analysis

Chi square and Independent sample Student's *t*-tests respectively were used to test for differences in gender and age among the groups. Independent sample Student's *t*-tests were also used to test for group differences on the SHAPS, AMSR, and cue response task. Regions of interest (ROI) were identified for fNIRS analysis in bilateral RPFC and VLPFC based on prior findings (Bunce et al., 2012; Bunce et al., 2015; Zijlstra et al., 2009). For fNIRS data, optodes were analyzed using independent Student's *t*-tests comparing PODP and controls on mean oxygenated hemoglobin in response to each positive stimulus category (food, social, and intimate) minus neutral blocks. For BA 10, the *a priori* region-of-interest (ROI) contrasts were thresholded at $P < 0.05$; regions outside of the defined ROI were thresholded at $P < 0.03$. All statistical analyses were conducted with SPSS 21.0.0 (IBM SPSS Statistics).

3. Results

3.1. Demographic information and questionnaire data

PODP did not differ from controls in age ($t(46) = -1.2$, NS) or gender (X^2 (2) = .87, $n = 46$, NS; see Table 1). A Student's *t*-test revealed that PODP reported higher scores on the SHAPS ($M = 1.56$; SD = 2.1) relative to controls ($M = .2$; SD = .4), suggesting greater levels of anhedonia among the patients on the day of testing $t(44) = -3.55$, $p < .01$.

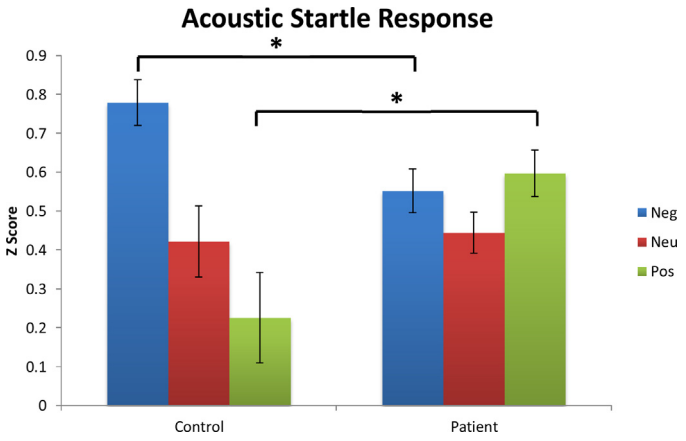

Fig. 2. Recently withdrawn prescription opiate dependent patients (PODP) display dysregulated processing of emotionally valenced stimuli via affect-modulated acoustic startle response. Response to negative stimuli is significantly lower ($p < .05$) for PODP and response to positive stimuli is significantly higher ($p < .05$). Neg: negative stimuli; Neu: neutral stimuli; Pos: positive stimuli; *: $p < .05$ error bars: SEM.

3.2. AMSR

Inspection of the means from the startle response task revealed that control participants showed the expected pattern of results in response to negative, neutral, and positive stimuli (e.g., Bradley et al., 1999; see Fig. 2). As predicted, PODP showed less startle suppression (i.e., greater positive amplitude) than controls when viewing positive stimuli ($t(40) = -2.87$, $p < .01$), consistent with a less positive evaluation of the stimuli. Patients were found to have lower startle amplitude in response to the negative stimuli relative to controls ($t(40) = 2.03$, $p < .05$), suggesting a less negative appraisal of these stimuli.

3.3. Cue reactivity and fNIRS

As expected, PODP ($M = -.072$, SD = .12) relative to controls ($M = .02$, SD = .12), displayed reduced neural activation to images depicting positive social interactions in left VLPFC (corresponding to Optode 1; see Fig. 3a ; $t(40) = 2.04$, $p < .05$). PODP ($M = -.07$, SD = .15) were also found to have reduced neural activation to images depicting highly palatable food relative to controls ($M = .01$, SD = .06) in left lateral RPFC/VLPFC (Optodes 2, 3, 4 see Fig. 3b; $t(42) = 2.6$, $p = .01$); right VLPFC (Optode 16; Fig. 3b; PODP ($M = -.12$, SD = .18) versus controls ($M = .05$, SD = .11); $t(40) = 2.39$, $p = .02$), and left medial RPFC (Optode 7; Fig. 3b; $M = -.09$, SD = .15 versus controls ($M = .03$, SD = .08; $t(39) = 2.24$, $p = .03$)), No differences were found in response to the emotionally intimate images.

Patients and controls showed evidence of differential responses to food and social stimuli consistent with anhedonia in patients. To further refine the relationship between self-reported anhedonia and the neuroimaging data, patients were categorized into two groups based on their response to the SHAPS. Patients were defined as anhedonic if they scored greater than 2 on the SHAPS (as defined by Snaith et al., 1995); those who scored 2 or less were considered to have normal hedonic tone. ROI analyses of lateral RPFC indicated that patients self-reporting anhedonia ($n = 14$) showed reduced neural activation in response to social stimuli relative to patients failing to report anhedonia ($n = 22$). More precisely, patients reporting anhedonia showed relatively less activation in right medial/lateral RPFC and right lateral RPFC when viewing social stimuli (Optodes 3, 4, 5, and 6; $t(28) = 2.32$, $p = .03$; and Optodes 9, 11, 12, and 13; $t(28) = 2.32$, $p = .03$; see Fig. 4a). Relative to patients who did not report anhedonia, patients who did report anhedonia showed reduced neural activation in left lateral RPFC (optodes 5 and 7) when viewing food-related stimuli $t(28) = 2.33$, $p = .03$. No differences in neural activity were found between patients reporting versus not reporting anhedonia in response to the emotionally intimate stimuli.

4. Discussion

This study used three separate measures that, taken together, offer evidence that some degree of anhedonia is present among prescription opiate-dependent patients in the early stages of recovery. Relative to control participants, PODP endorsed higher levels of anhedonia on a validated self-report instrument of hedonic tone the day of neurophysiological testing. PODP were also found to have an affect-modulated startle response indicative of a less positive hedonic evaluation of putatively positive images relative to controls. Finally, when participants were viewing images depicting highly palatable food and positive social interactions, we found reduced neural activity among anhedonic patients in areas of bilateral rostral prefrontal cortex, consistent with those reported by Zijlstra et al. (2009). Together, this evidence supports the hypothesis that, following withdrawal from prescription opiates, a significant number of individuals experience an anhedonic state that may reduce their capacity to derive gratification from such natural rewards as positive social interactions and highly palatable food. This finding is consistent with a growing literature emphasizing the role of anhedonia in substance use disorders, particularly within the early stages of abstinence (e.g., Garfield et al., 2014; Hatzigiakoumis et al., 2011; Janiri et al., 2005).

To our knowledge, the current study is the first to examine neural responses to distinct categories of positive/natural reward stimuli in a population of prescription opiate dependent patients. Of particular interest, PODP endorsing self-reported anhedonia showed reduced activation to positive social images in both right and left lateral RPFC relative to patients who did not endorse anhedonia. Food showed a similar pattern, but was limited to the left lateral RPFC. Rostral PFC has been shown to be involved in a wide range of tasks (Gilbert et al., 2006). The area of RPFC activated by the social stimuli has been shown to be involved in the retrieval of episodic memories, and to a lesser degree, emotional material. It is possible that activation in this area may be associated with the process of linking social stimuli and food to episodic memories. This interpretation would suggest these positive memories may be less available to anhedonic patients. Similarly, with regard to the AMSR, we found that PODP exhibited larger startle responses to positive stimuli relative to controls (see Fig. 2), indicative of a more negative evaluation of the stimuli (Bradley et al., 1999). This evidence suggests that viewing positive stimuli likely does not elicit the positive feelings, or evoke the positive memories, among PODP that it does among the healthy controls. Further research is needed to understand the exact nature of these responses in anhedonic patients.

Interestingly, emotionally intimate stimuli did not elicit group differences in the prefrontal areas that were monitored. One hypothesis is that emotional intimacy may elicit more complex emotions and memories than palatable food or even non-intimate positive social situations among PODP, as well as among control populations. Individual differences in patient response to emotionally intimate stimuli, rather than group differences, may still be related to vulnerability to relapse. Alternatively, more individualized stimuli, or imaging other brain areas may be necessary to understand the role of emotionally intimate imagery in anhedonic patients.

As 22 of 36 patients (61%) did not meet previously established criteria for clinically relevant anhedonia on the SHAPS (vs 0% among controls), it is likely that there are significant individual

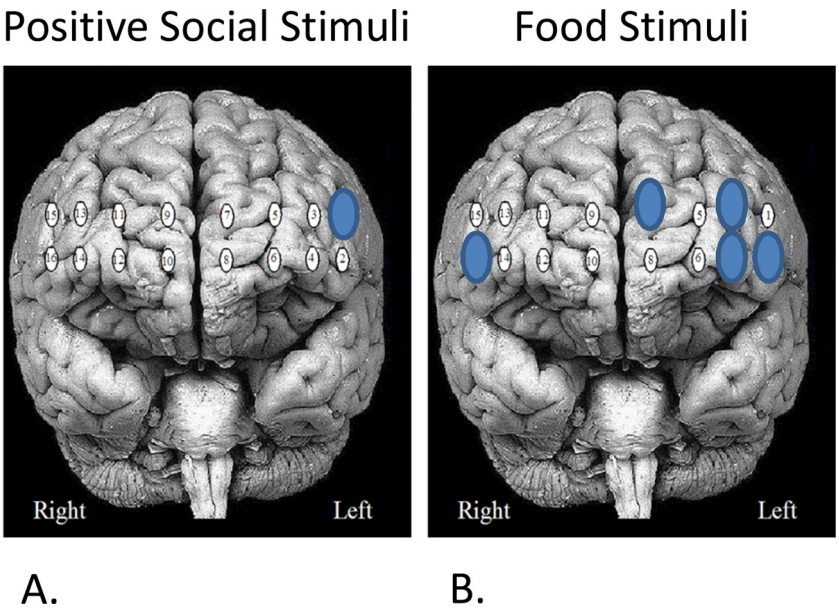

Fig. 3. Recently withdrawn opiate-dependent patients show reduced activation to visual stimuli compared to healthy controls. Each number represents an optode on the functional near-infrared spectroscopy sensor; blue dots correspond to areas of decreased activity ($p < .05$).

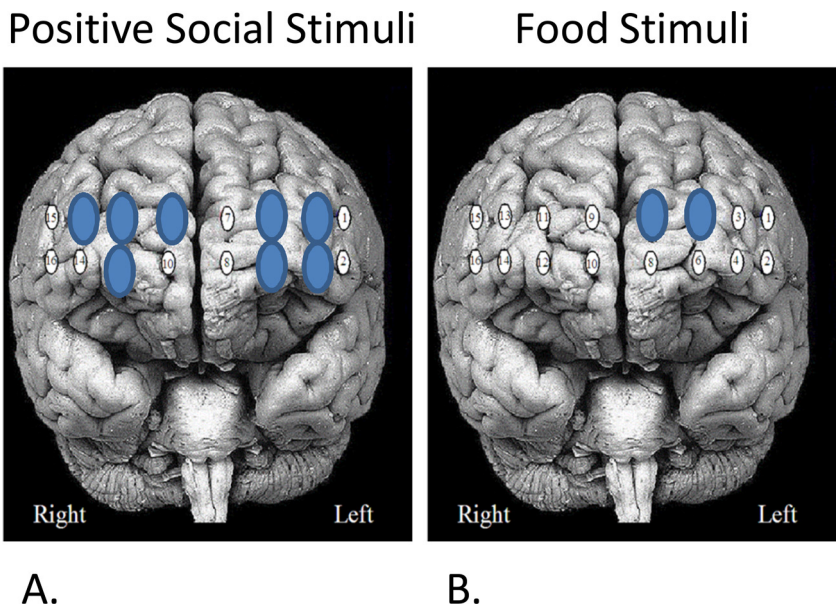

Fig. 4. Recently withdrawn opiate-dependent patients split into two categories: patients self-reporting anhedonia (as evident by score > 2 on the Snaith–Hamilton Pleasure Scale), and patients not endorsing anhedonia. When comparing these two sub-groups, patients self-reporting anhedonia show reduced activation to social and food stimuli. Each number represents an optode on the functional near-infrared spectroscopy sensor; blue dots correspond to areas of decreased activity ($p < .05$).

differences in anhedonia in this patient population. These individual differences are of particular interest, as greater anhedonia should theoretically be associated with greater risk for relapse. The inherent limitations of self-report instruments, however, make it likely that the outcome of the SHAPS, while informative, may not accurately characterize every patient with regard to clinically relevant anhedonia. Like the construct of craving, the measurement of anhedonia may benefit from conceptualization as a multidimensional phenomenon with subjective, behavioral, physiological, and neurochemical correlates. Just as neuroimaging techniques – coupled with cue-induced craving – have been shown to be a better predictor of treatment outcomes than self-reported craving (e.g., Goldstein et al., 2009; O'Brien, 2012), the current data suggest a similar approach may be warranted for the construct of anhedonia. The multifaceted methodology used in this study represents an initial approach to a clinically relevant assessment of anhedonia. Further longitudinal research, evaluating anhedonia in conjunction with measures of negative affect, drug craving, stress, and HPA axis functioning (e.g., sleep, cortisol) over time in abstinence, would be necessary to fully elucidate the role of anhedonia in vulnerability to relapse. Repeated measures in longitudinal studies of abstinent patients would also help to clarify the timecourse and proportion of patients that might show evidence of hedonic reregulation.

There are several limitations to the current study. First, the study is cross-sectional. Whereas it is possible to identify neural correlates of purported anhedonia, it cannot be determined if these measures are valid predictors of treatment response or treatment outcome, and further research is necessary. Second, it cannot be

determined from these data whether the anhedonic state found in these patients is the function of an allostatic process related to drug use (e.g., Koob and Le Moal, 2001; Pettorruso et al., 2014), or a pre-existing condition that may have played a role in the onset of addiction (e.g., Blum et al., 2000; Loas, 1996). In either case, the compromised capacity to derive pleasure from natural rewards among the anhedonic patients is likely to have an impact on their efforts to remain drug-free. However, efforts to improve treatment in addiction might benefit from a more refined understanding of the etiology of anhedonia in substance use disorders. Medications that show efficacy for symptoms of depression are not always effective for anhedonia (Di Giannantonio and Martinotti, 2012). Efforts to develop medications (e.g., Di Giannantonio and Martinotti, 2012; Martinotti et al., 2011) or neuro-nutrient therapies (Blum et al., 2012) that target anhedonia may benefit from the utilization of valid, affordable, and objective measures of hedonic tone that could be implemented in both research and clinical settings. Third, there are a number of different measures of anhedonia (Franken et al., 2007; Garfield et al., 2014), which might produce different results. As in much of psychiatry, there is currently no gold standard for the assessment of anhedonia, which places an emphasis on developing objective measures with clinical relevance.

5. Conclusion

This study addressed several timely questions concerning the presence of anhedonia among individuals in the early stages of recovery from prescription opioid dependence. Our data suggest that some, but not all, PODP showed evidence of reduced response to stimuli depicting natural rewards in this stage in treatment. Further longitudinal research is necessary to address questions regarding the impact of anhedonia on the processes of recovery and relapse. Previous studies suggest that, post withdrawal, anhedonia decreases over time, and that reduction in anhedonia is related to reduction in drug craving (Janiri et al., 2005). However, further research is needed to determine the nature and time-course of the potential reversal of allostatic processes in substance use disorders. Further research is also needed to more fully explore the relationship between anhedonia, drug related craving responses, and the risk of proximal relapse following discharge from residential treatment. Finally, our results suggest that further multimodal research on the construct of anhedonia is warranted, including assessments of its clinical utility.

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