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Differential effects of short-term morphine treatment on brain volumes of men and women with low back pain

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DIFFERENTIAL EFFECTS OF SHORT-TERM MORPHINE TREATMENT ON BRAIN VOLUMES OF MEN AND WOMEN WITH LOW BACK PAIN

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ABSTRACT

Objective: Long- and short-term opioid use is associated with morphological changes in the human brain. Opioids have analgesic and adverse effects, including addiction, that differently impact men and women. The current study aimed to investigate whether differences exist between men and women in gray matter volume changes after acute morphine treatment for chronic low back pain.

Methods: This study analyzed data from 27 chronic low back pain patients (17 men, 10 women) who were treated with oral morphine over a period of 30 days. High-resolution structural images were acquired immediately before and after morphine treatment. Images were compared using voxel based morphometry. Differential regions of gray matter change in men and women were tested for correlation with morphine dosage and other behavioral measures such as pain reduction.

Results: There were no significant morphological differences between men and women in selected pain processing- and reward-related regions of interest. Whole brain analysis, however, revealed differential changes in gray matter of the left dorsolateral prefrontal cortex (dlPFC), right middle frontal gyrus (MFG), and left insula. These differences were not significantly correlated with morphine dosage or behavioral measures.

Conclusions: This study is the first to assess morphological differences between men and women over a course of opioid treatment. We found that there were no significant differences in the impact of opioids on selected reward-related regions of interest.

Therefore, men and women may be at an equal risk for addiction to opioid medication. However, there are brain areas where men and women differ in response to opioids. These findings warrant future research.

Keywords: opioids, sex differences, magnetic resonance imaging, voxel based morphometry

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Introduction

Opioid analgesics are among the most commonly prescribed medications in the United States [1, 2]. Between 1999 and 2010, sales of prescription opioids in the United States increased by 300% [1]. In addition to their beneficial therapeutic properties, opioid use can be associated with limiting side effects such as constipation, hyperalgesia, behavioral and cognitive changes, addiction, and overdose [3]. These adverse events are becoming prominent issues in public health alongside climbing rates of use [1]. There is, therefore, a need to determine the risk factors of adverse opioid events. One such predictive factor may be biological sex [2].

There are many behavioral differences between women and men regarding opioid use. Between 2007 and 2012, use of prescription opioid analgesics was higher among women than men over the age of 19 years (7.2% vs. 6.3%, respectively), reflecting a greater tendency for women to receive opioid prescriptions, and at generally higher doses [1, 4, 5]. This phenomenon may be related to the fact that many chronic pain conditions – e.g. fibromyalgia, temporomandibular syndrome, and irritable bowel syndrome – are diagnosed more commonly in women [3, 6-9]. Between 1999 and 2010, overdose deaths involving prescription opioids increased by 400% in women and 265% in men [1, 10]. However, men are overall more likely to experience serious negative outcomes of opioid use such as emergency department visits and overdose death [11-13].

Given these differences, clinical exploration highlighting sex-based opioid effects and consequential health risks is warranted. However, the vast majority of clinical and pre-clinical research on pain and analgesia to date has focused on males. Of the limited research available, notable differences in behavioral responses to opioids have been

revealed. The majority of evidence from pre-clinical pain studies supports greater morphine analgesia in male versus female rodents [14]. Indeed, the median effective dose of morphine in females is estimated at approximately twice the dose necessary for males [15]. Clinical research on analgesic effects of morphine in humans is limited and less consistent than pre-clinical reports. While some clinical studies report greater analgesia in women, others report the opposite or even statistically equivalent analgesia [16-19]. Retrospective studies of post-operative morphine use reveal that men consume more than women. However, rate of opioid use does not necessarily correspond to actual analgesia, as women are more likely to experience exacerbated side effects of morphine such as nausea, headache, and dysphoria [15, 18, 20].

Risk for addiction and other opioid-related changes may be captured by imaging studies. Seifert and colleagues (2015) found that individuals who were chronically heroin-dependent showed decreased gray matter volume in the left nucleus accumbens (NAcc) compared to healthy, opioid-naïve controls. The nucleus accumbens is an integral structure in the brain's reward system and has an important role in drug dependence [21]. Upadhyay and colleagues (2010) found that prescription opioid-dependent patients had relatively decreased gray matter volume in the bilateral amygdala [22]. Our group similarly found volumetric decreases in the amygdala with just one month of morphine use. Greater degree of volume loss was associated with greater opioid craving after cessation, perhaps indicating the early neuroplastic changes involved in addiction [23]. To date, no human sex difference studies of opioid effects on the brain have been carried out. Prior literature highlights exacerbation of deleterious side effects and potential decrease of analgesic potency in women [2, 3]. Men, on the other hand, continue to

exhibit higher abuse and incidence of negative outcomes related to opioids [1]. These effects suggest that women and men may be differently affected by opioids at the brain level.

The current study aims to investigate differences between men and women in gray matter volume changes after 30 days of morphine treatment for chronic low back pain. Given our previous findings of morphological changes with morphine treatment, we expect to find differential volumetric changes in men versus women in the amygdala. We expect that differential volumetric changes may also be found in other reward-related structures, i.e. NAcc, ventral tegmental area (VTA), and bed nucleus of stria terminalis (BNST) [21, 24, 25]. Additionally, specific to previous pre-clinical findings of sexually dimorphic pain and opioid-related circuitry, we expect to see differential changes in the periaqueductal gray (PAG).

Methods

The overall design of this double-blind, longitudinal, pre-post neuroimaging study included random assignment of participants to two groups: morphine treatment or non-active placebo. Full details of this design have been previously reported [23]. This study contains previously reported data from 19 participants and additional data from 8 participants, all of whom were assigned morphine treatment.

Participants

Twenty-seven participants (17 men, 10 women) with moderate to severe, nonradicular, chronic low back pain completed the study. Participants were eligible for enrollment in the study if they were between 18 and 70 years of age and were candidates for chronic opioid therapy for nonmalignant pain. These were individuals who had not

responded adequately to non-opioid treatments. Participants were excluded on the basis of previous opioid use, history of substance abuse, unstable psychiatric condition, evidence of neuropathic pain, prescription for neuropathic pain medication, or a positive urine pregnancy test at the time of enrollment. Participants were permitted to continue use of over-the-counter analgesics for the duration of the study. All study procedures were approved by the Institutional Review Board (IRB) at Stanford University of Medicine, and continued data analyses were approved by the IRB at the University of Alabama at Birmingham. Written informed consent was obtained from all participants.

Morphine Treatment

Participants received titrated doses of morphine over a 30-day period. A double-encapsulated, sustained-release, oral formulation of morphine was used (MS-Contin; Purdue Frederick, Stamford, CT, USA). All participants received an initial dose of 15 mg (one capsule), twice daily. Dosage was increased every other day by 15 mg until (1) adequate analgesia was achieved, (2) side effects prevented further increases, or (3) an upper maximum dosage of 120 mg/day was reached. Morphine doses were taken no more than three times per day with no more than 45 mg per administration. For ethical and medical safety reasons, doses of morphine were not randomly assigned. Total morphine exposure ranged from 915 mg to 2970 mg (mean 2361 mg) over the 30-day period.

Pain Assessment

The Brief Pain Inventory (BPI) was used to assess the analgesic effect of morphine on chronic low back pain [26]. The BPI collects information on pain severity, impact of pain on daily functioning, location of pain, current pain medications, and amount of pain relief experienced over the past 24 hours. On the pain severity subscale,

participants indicated current pain and worst, least, and average pain experienced over the past 24 hours. The numerical rating scale ranges from 0 - "No pain" to 10 - "Pain as bad as you can imagine." The average of the four pain intensity ratings was used as a measure of chronic pain severity for each participant, assessed before and after the 30 days of morphine treatment. The impact of pain on daily functioning was assessed via ratings of the degree to which pain has interfered with general activity, mood, walking ability, work, interpersonal relations, sleep, and enjoyment of life over the past 24 hours. The numerical rating scale ranges from 0 – "Does not interfere" to 10 – "Completely interferes." The average of the seven interference ratings was used as a measure of impact of pain on daily functioning.

Emotional Status

The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of anxiety and depression before and after morphine treatment [27].

Image Acquisition

Magnetic resonance imaging (MRI) data were collected at the Richard M. Lucas Center for Imaging at Stanford University on a 3.0 Tesla GE Healthcare Discovery 750 (GE Signa, Milwaukee, WI) with an 8-channel head coil. A T1-weighted 3D inversion recovery-prepared fast spoiled gradient-recalled (IR-FSPGR) scan was acquired with the following parameters: axial slices, repetition time = 7.2 ms, echo time = minimum, flip angle = 11°, 128 slices, slice thickness = 1.2 mm, field of view = 220 x 220 mm, matrix = 256 x 256 voxels. A voxel resolution of 1.2 x 0.86 x 0.86 mm was acquired. All participants completed a scanning session before and after the 30-day morphine treatment.

Image Analysis Procedure

Structural brain images were processed using a voxel based morphometry (VBM) technique with SPM12 software (Wellcome Trust Centre for Neuroimaging, London, UK) executed in MATLAB (MathWorks, Natick, MA, USA). All scans were normalized to Montreal Neurological Institute (MNI) template space with Diffeomorphic Anatomical Registration using Exponential Lie Algebra (DARTEL; [28]). Normalized images were resampled using 1.5 mm isotropic voxel size. Images were then segmented and smoothed with a 2 mm Gaussian isotropic kernel.

Statistical Analyses

In order to identify differential morphine-induced gray matter volumetric changes, whole brain analyses were performed on all participants using a mixed-effects model. Due to small sample sizes, nonparametric permutation statistics were run utilizing the Statistical NonParametric Mapping toolbox (SnPM13) in SPM12 [29]. A Flexible Factorial model was used with 2 factors: group (men or women) and time (pre-morphine or post-morphine). First, morphological changes were assessed within each participant, comparing pre-morphine to post-morphine scans. Next, the model identified group-level differences in morphological change between men and women. A significance threshold of $p < 0.0005$ (uncorrected) was used, and a separate cluster threshold of 10 voxels was used to further reduce false positives.

Regions of interest analyses were performed in reward-related structures and structures identified by previous clinical and pre-clinical research to be involved in morphine exposure and/or sexually dimorphic pain and opioid-related circuitry. These

regions included bilateral amygdala, nucleus accumbens, and brainstem as identified by the Hammers brain atlas [30].

The relationship between volumetric changes, morphine exposure, and self-report measures was investigated with a two-tailed Spearman's rho. Areas of significant gray matter change between groups were tested for association with morphine dosage (mg/kg) and change in pain intensity, functional ability, anxiety, and depression.

Results

Demographics

One participant (female) was excluded from analyses because she was able to tolerate a total morphine dosage of only 165 mg due to negative side effects. The remaining 26 participants (9 women, 17 men) were included in all final analyses. Overall, women and men did not differ in average total dosage of morphine by weight (women: 25.3 ± 11.4 mg/kg; men: 25.4 ± 6.6 mg/kg). In addition, women and men did not differ significantly in duration of low back pain (women: 10.3 ± 11.2 years; men: 10.1 ± 7.9 years). They did, however, differ in age (women: 47.8 ± 12.5 years; men: 38 ± 9.9 years; $t(24) = 2.188$, $p = 0.04$). All behavioral variables are reported in Table 1.

Pain Assessment

Mean pain intensity prior to morphine treatment was 4.58 ± 1.08 for women and 3.97 ± 0.96 for men. There was no statistically significant main effect of group ($F(1,24) = 1.667$, $p = 0.209$). There was a significant main effect of time ($F(1,24) = 30.485$, $p < 0.001$) such that overall intensity of pain decreased following 30 days of morphine treatment for both women and men. The interaction of group * time was not significant ($F(1,24) = 0.106$, $p = 0.748$), indicating similar rate of pain reduction between women

and men.

The effect of pain intensity on functional ability was not significantly different between groups ($F(1,24) = 2.130$, $p = 0.157$). Mean interference of pain on everyday function was 2.78 ± 2.35 for women and 2.08 ± 1.34 for men. Main effect of time was significant ($F(1,24) = 16.299$, $p < 0.001$) such that the interference of pain on everyday function was reduced following treatment. The group * time interaction was not significant ($F(1,24) = 0.469$, $p = 0.500$), indicating a similar pattern of reduction in pain interference between women and men.

Emotional Status

Prior to morphine treatment, women scored an average of 4.22 ± 3.93 and men scored an average of 4.24 ± 2.59 on the anxiety scale of the HADS. On the depression scale of the HADS, women scored an average of 4.22 ± 4.24 and men scored an average of 2.53±1.81. Overall, baseline scores fell below the cutoff for anxiety or depression. Women and men did not significantly differ in anxiety or depression scores ($F(1,24) = 0.006$, $p = 0.941$ and $F(1,24) = 2.684$, $p = 0.114$, respectively). The main effect of time was not significant for anxiety scores ($F(1,24) = 2.664$, $p = 0.116$), but was significant for depression scores ($F(1,24) = 4.716$, $p = 0.040$) such that symptoms of depression decreased over time for both women and men. There was no significant interaction of group * time ($F(1,24) = 0.042$, $p = 0.840$ and $F(1,24) = 0.004$, $p = 0.951$, respectively).

Imaging Results

Morphological changes observed in response to one month of oral morphine use differed between men and women in three areas. Volumetric decreases were observed in the left dorsolateral prefrontal cortex (dlPFC) and right middle frontal gyrus (MFG) of

women compared to men. Conversely, volumetric decreases were observed in the left insula of men compared to women (Table 1; Figure 1). There were no significant differences between groups in specified regions of interest: bilateral amygdala [left: $t(24) = 0.259$, $p = 0.798$; right: $t(24) = 0.011$, $p = 0.991$], nucleus accumbens [left: $t(24) = 1.454$, $p = 0.159$; right: $t(24) = 1.696$, $p = 0.103$], and brainstem [left: $t(24) = 1.086$, $p = 0.288$; right: $t(24) = 1.318$, $p = 0.200$].

Volumetric changes between groups were not significantly associated with morphine dosage, percent change in average pain intensity, percent change in average interference of pain on daily functioning, or change in symptoms of anxiety or depression. Because men and women participants differed in age, separate statistical analyses were run controlling for age as a covariate. No additional significant results were found. It is unlikely that age would explain behavioral or morphological differences observed over a month of morphine treatment. All correlations are reported in Table 2 without including age as a covariate.

Discussion

While most clinical studies on opioid analgesics have not explored the potential influence of biological sex, there is some evidence that men and women differ in how they experience both the analgesic properties and unwanted side effects of opioids [15, 18, 20]. There is also evidence that endogenous opioid and pain processing systems differ in a sex-dependent manner, highlighting potential underlying involvement of the central nervous system [2]. Our group has previously shown that prescriptive oral morphine can rapidly change the brain, and that these changes persist even 4.7 months beyond cessation of morphine treatment [23, 31]. Differences in morphine-associated morphological

changes between men and women may explain differential behavioral reactions to opioids and differential patterns of substance dependence and risk for addiction.

The primary aim of our analyses was to determine whether one month of daily oral morphine use differentially affects brain volumes of women and men with chronic low back pain. We hypothesized that regions of the brain involved in reward and processing of pain and opioid analgesia would be differentially affected in men and women. However, our results did not reveal significant morphological changes in the amygdala, NAcc, or brainstem between groups. We also aimed to determine whether groups differed on behavioral measures associated with pain treatment. We found that men and women did not exhibit significant differences in morphine dosage, pain reduction, or decreased emotional distress. These findings challenge previous evidence that women may require higher opioid dosages to achieve equivalent analgesia as compared to men [14, 15].

Although we did not discover differential volumetric changes in traditional areas of reward and opioid-related circuitry, whole brain analyses revealed three notable regions of change: the left dlPFC, left insula, and right MFG. While changes in these structures were not significantly associated with morphine dosage, pain reduction, or decreased emotional distress, we believe that they may play a role in alternative aspects of reward and pain-related processes.

For example, the dlPFC is involved in behavioral inhibition, impulsivity, and risk-related processing [32, 33]. The frontal lobes are considered centers of inhibition and damage to the prefrontal cortex is associated with motivational/emotional disinhibition [32, 34-36]. Impulsivity or deficient inhibitory control has been identified as a risk factor for drug addiction and is considered the primary behavioral characteristic of drug abusers

[32, 37-40]. In a meta-analysis by Gowin, Mackey, and Paulus (2013), the authors identified differential neural activity during risk-taking between individuals with substance use disorders and healthy controls in the anterior cingulate cortex, orbitofrontal cortex, dlPFC, striatum, insula, and somatosensory cortex [33]. The right MFG is also involved in executive functioning and cognitive control processes, including successful response inhibition [41, 42]. In our study, the left dlPFC decreased in volume by 2.3% in women and increased by 6.3% in men. The right middle frontal gyrus decreased in volume by 6.8% in women and increased by 3.8% in men. These changes may underlie potential differences in cognitive control functions between men and women following acute opioid use. However, this cannot be determined in the present analyses.

The insula is associated with processing of noxious stimuli [43-49]. Lorenz, Minoshima, and Casey (2003) found a significant increase in activity in the anterior insula associated with heat allodynia [50]. Bilateral anterior insula showed selective correlation with unpleasantness of heat stimuli. It is proposed that the anterior insula assist in decoding intensity of noxious stimuli [50-52]. In the current analyses, the left insula increased in volume by 5.8% in women and decreased by 3.4% in men. While volumetric changes were not significantly associated with pain reduction, the opposite directions of change may highlight differential pain processing in men and women.

There are a few limitations to this study which must be considered. First, this study included a relatively small group of women participants (9 women versus 17 men) and participants were not matched by age. Therefore, the results should be interpreted with caution and require future studies to determine generalizability. Second, while this study revealed differential volumetric changes in areas relevant to behavioral and cognitive

effects associated with opioid use, specific measures were not included to explore this relationship. Future studies should incorporate behavioral measures related to the rewarding effect of opioid medications (such as drug-liking and drug-craving) and cognitive measures related to risk-taking and response inhibition. Third, although there has been evidence that women more frequently experience unwanted side effects of opioid treatment than do men, we did not include a formal measure of effects such as constipation, nausea, headache, and dysphoria. Side effects were informally monitored to determine maximum tolerated daily dosage. Finally, this study measured brain and behavioral changes occurring over only one month of morphine treatment. An interesting future study might monitor brain and behavioral changes at multiple time points over the course of extended opioid therapy for chronic pain. This would allow for exploration of associations between differential brain changes and progression of opioid therapy with regard to analgesic effects, side effects, and potential developing dependence.

This study is the first to assess longitudinal morphological differences between men and women over the course of acute opioid treatment. Generally, we found that there are no significant differences between men and women in the impact of opioids on reward-system structures. Therefore, men and women may be at an equal risk for addiction. However, there are discrete brain areas where men and women differ in response to opioids. These findings warrant future research. The behavioral implications of these differential brain changes should be explored to better understand the clinical impact of opioid medications on men and women. Future studies may explore the appropriateness of opioid medications for chronic pain treatment based on sex. Additional research may help to determine the therapeutic benefit of opioid medications in terms of analgesic

efficacy and negative side effects, as experienced differentially by men and women.

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	Women (n=9)	**Men (n=17)**		
Age (years)	47.8 ± 12.5	38 ± 9.9		
Pain Duration (years)	10.3 ± 11.2	10.1 ± 7.9		
Total Morphine (mg/kg)	25.3 ± 11.4	25.4 ± 6.6		
Pain Intensity (% change)	-48.1 ± 49.9	-44.9 ± 60.8		
Pain Interference (% change)	-45.2 ± 41.5	-62.8 ± 36.7		
HADS Anxiety	-0.78 ± 1.56	-1.0 ± 3.04		
HADS Depression	-1.0 ± 3.39	-1.06 ± 1.48		
Imaging Results	**Volume Change**		**MNI Coordinates**	***T*-value**
L dorsolateral PFC	-2.3%	+6.3%	-40.5, 45, 28.5	-2.93
L insula	+5.8%	-3.4%	-27, 19.5, 7.5	5.84
R middle frontal gyrus	-6.8%	+3.8%	40.5, 15, 57	-3.93

Table 1. Demographic Characteristics and Imaging Results. Demographic and self-report variables presented as mean ± standard deviation (SD). All listed volumetric changes are significant below the *p*-value threshold 0.0005.

		Women (n=9)			Men (n=17)		
		L dlPFC	L insula	R mid frontal	L dlPFC	L insula	R mid frontal
Total Morphine (mg/kg)	r_s	0.083	0.267	-0.017	0.032	-0.171	0.000
	p	0.831	0.488	0.966	0.905	0.528	1.000
Pain Intensity (% change)	r_s	-0.033	0.133	0.117	-0.388	-0.450	0.029
	p	0.932	0.732	0.765	0.137	0.080	0.914
Pain Interference (% change)	r_s	-0.450	0.267	-0.350	-0.284	-0.427	-0.113
	p	0.224	0.488	0.356	0.286	0.099	0.676
HADS Anxiety	r_s	0.732	0.136	0.604	-0.436	-0.034	-0.250
	p	0.025	0.727	0.085	0.092	0.901	0.350
HADS Depression	r_s	-0.059	-0.397	0.093	-0.424	0.149	0.018
	p	0.880	0.291	0.812	0.102	0.582	0.947

Table 2. Behavioral Variables and Regional Volumetric Changes. Spearman's rho (r_s) correlations between significant regions of differential change, morphine exposure, and self-report measures. No correlations survived the false discovery rate (FDR)-corrected significance level $p < 0.0151$.

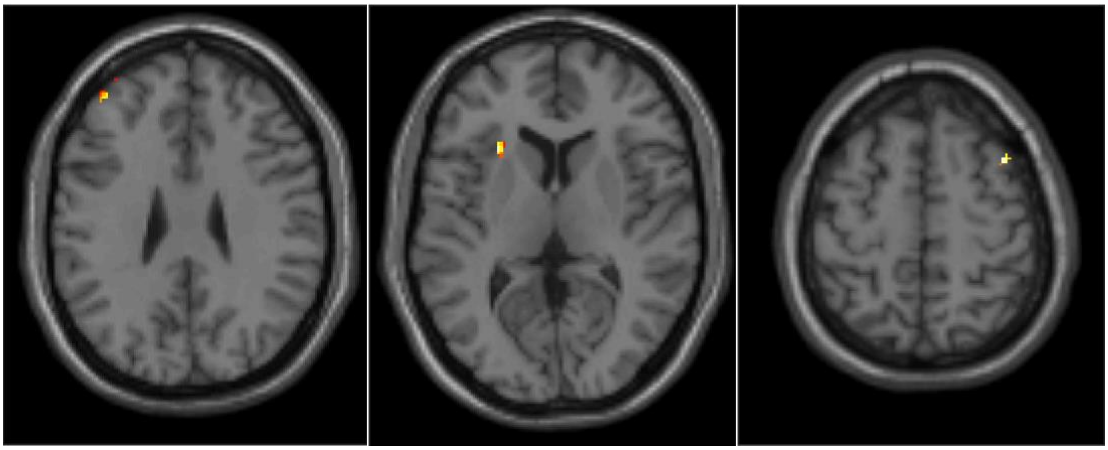

Figure 1. Differential Volumetric Changes. Significant gray matter changes between women and men following 30 days of morphine treatment. From left to right: left dorsolateral prefrontal cortex (z = 28.5), left insula (z = 7.5), right middle frontal gyrus (z = 57).

APPENDIX

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

MEMORANDUM

TO: Jarred W Younger, PhD
Principal Investigator

FROM: Nancy I Stansfield, RN, MSN, CIP
On behalf of IRB 02

DATE: December 3, 2015

RE: F141001001
Neuroimaging of Pain

The IRB 02 met on **December 2, 2015** and **approved** the protocol referenced above. The approval form and three IRB-stamped consent forms are attached. **This approval will expire and no longer be valid on December 2, 2016.**

Please note the following as related to this review:

- The IRB reviewed and approved the changes requested in Item 10 of the Investigator's Progress Report.
- The IRB has updated several forms including the Human Subject Protocol, Investigator's Progress Report, sample consent form, and checklists for convened and expedited original submissions and renewals. The updated forms are available at www.uab.edu/irb, along with a description of the updates. At the next submission, use the most recent version of the forms. As of September 1, 2015, the most recent version of the forms is required.
- All key research personnel who completed initial human subjects training before January 1, 2015 are required to complete one of the following UAB IRB continuing training courses prior to December 31, 2015. Key research personnel must complete either "IRB Continuing Training (CITI Refresher Course) - Biomedical 2015" or "IRB Continuing Training (CITI Refresher Course) - Social/Behavioral/Educational 2015", as appropriate. Refer to the IRB website at www.uab.edu/irb/training/continuing for information regarding this requirement. This continuing training meets the requirement for the 2015 – 2017 training period.

NIS/ccs

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	YOUNGER, JARRED W
Co-Investigator(s):	CAMPBELL, KELSEY A
Protocol Number:	**F141001001**
Protocol Title:	*Neuroimaging of Pain*

The IRB reviewed and approved the above named project on 12/2/2015. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 12/2/2015

Date IRB Approval Issued: 12-3-2015

IRB Approval No Longer Valid On: 12-2-2016

Identification Number: IRB00000726

Albert Oberman MD MPH (M.S.)

Albert Oberman, M.D., MPH
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Partial HIPAA Waiver Approved?: Yes

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Institutional Review Board for Human Use

PI: YOUNGER, JARRED W
Protocol # F141001001

UAB IRB Approval of
Partial Waiver of HIPAA Authorization
to Use PHI in Screening for Research

☑ **Patient Authorization: Approval of Partial HIPAA Waiver to Use PHI in Screening for Research.** The IRB reviewed the proposed research and granted the request for a "partial HIPAA waiver," to allow the proposed use of protected health information (PHI) in screening for research, based on the following findings:

1. The use/disclosure of PHI to screen candidates for research involves no more than minimal risk to the privacy of individuals
   a. There is an adequate plan to protect the identifiers from improper use and disclosure.
   b. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
   c. The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The screening cannot practicably be conducted without the waiver or alteration.
3. The screening cannot practicably be conducted without access to and use of the PHI.

—OR—

☑ **Full Review**
The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The partial waiver of authorization for screening was approved by the majority of the IRB members present at the meeting.

12-2-2015
Date of Meeting

Albert Olvera MD (a.)
Signature of Chair, Vice-Chair or Designee

12-3-2015
Date

☐ **Expedited Review**
The IRB used an **expedited review procedure** because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the partial waiver of authorization for screening was carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

_____
Date of Expedited Review

_____
Signature of Chair, Vice-Chair or Designee

_____
Date

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