A Feasibility Study: Understanding and Altering Pain Expectations in Subjects with Osteoarthritis of the Knee or Hip

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Why a feasibility study

In May we submitted a Program Project Grant (P01) application to the NIH. This $10 million effort would fund a group of laboratory and clinical investigations to better understand and prevent the problem of chronic pain and disability after major surgery. Although we provided some preliminary data with that application, we expect that additional feasibility data will be required for the application to reach a level of priority high enough for funding. The current IRB application is to collect those feasibility data in time for a November, 2014 revision.

Both chronic pain and disability after total knee replacement surgery are predicted by negative cognitive-affective state, characterized by depression, anxiety, and a cognitive style dominated by catastrophizing. How this negative state results in chronic pain and disability is not known, but we hypothesize that it causes dysfunction of the release of the neurotransmitter, norepinephrine in several regions of the brain, mid-brain, and spinal cord that are important to many processes involved in recovery from surgery. In the P01 grant application we propose to test these circuits in animals and to study patients after total knee replacement as well as those with moderate daily pain and osteoarthritis who are not undergoing surgery. This protocol is to generate feasibility data for the osteoarthritis study in time for the Nov, 2014 revision, if it is needed.

Background

The locus coeruleus (LC) as a regulator of gain. The LC is a small collection of neurons in the pons which provides the exclusive or near-exclusive noradrenergic innervation to the cortex, spinal cord, and mid-brain. Although involved in many processes, the diffuse cortical projections from the LC are key regulators of gain of overall brain network function and response (Eldar, 2013). As opposed to amplification, which results in increased signals from all components of a complex circuit, increasing gain results in increased dominance of strong signals at the expense of weak signals (Figure 1). In humans, increased LC activity and inferred gain sharpens connectivity as determined by fMRI such that weak connections become weaker and strong connections become stronger (Eldar, 2013). That study compared learning with abstract versus visual tests, and showed that increased gain resulted in stronger reliance on the individual's preferred learning style. In other words, when gain was low, individuals learned by either style, visual or abstract, but when gain was high, they relied much more heavily on their preferred style. Those who rated themselves better as visual learners became even better at the visual learning tasks and worse at the abstract learning tasks under high gain conditions, whereas the abstract learners did the opposite. Thus, gain determines how much one applies their preferred mode of response to a stimulus, situation, or task.

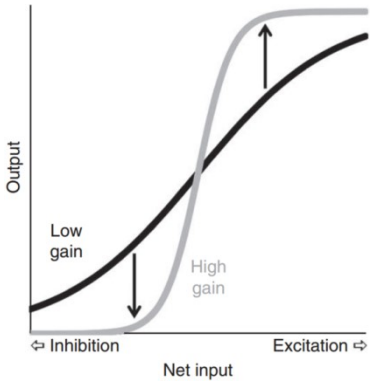

Figure 1: Gain sharpens output by altering input strength (Eldar, 2013)

Pain is a recurrent, powerful stimulus after surgery or in those with advanced arthritis, and the gain concept suggests that experience of intermittent pain reflects not just how the underlying personality factor interacts with the stimulus itself, but also how high the gain is. Data from an ongoing preliminary study in the CRU at Wake Forest in healthy volunteers receiving experimental pain stimuli support this idea.

The pupil reports LC activity and gain. Studies in animals with electrodes implanted in the LC and in humans with fMRI imaging of the LC suggest that changes in pupil diameter faithfully report LC activity (Gilzenrat, 2010; Payzan-Lenestour, 2013; Eldar, 2013). Our ongoing study in healthy volunteers asked how pupil responses could predict experience of pain from experimental stimuli.

In this ongoing study we have examined pupil responses to phasic noxious heat stimuli to date in 19 normal volunteers and 4 subjects with migraine (but not in the presence of a headache). Studies were performed in a room with constant, low ambient light so that both constriction and dilation of the pupil could be observed. Pupil diameter was continuous monitored by an infrared camera (Eye-Trac™ system; Applied Science Laboratories) with the subject's chin resting on a chin rest and gaze on a fixed object presented on a monitor. A 4 cm^2 Peltier-controlled thermode was placed on the calf, with temperature maintained at 35^0C and 5 sec stimuli at various temperatures applied every 30 sec. Subjects reported pain intensity with a visual analog scale (VAS) fro 0 (no pain) to 100 (worst pain imaginable). Increasing probe temperature to 50^0C resulted in pain report and pupil dilation, the former with a longer lag (Figure 2, typical response). As previously described with other stimuli (Chapman, 1999; Oka, 2007), there was a direct relationship between pupil dilation and noxious heat temperature as well as VAS pain intensity and unpleasantness.

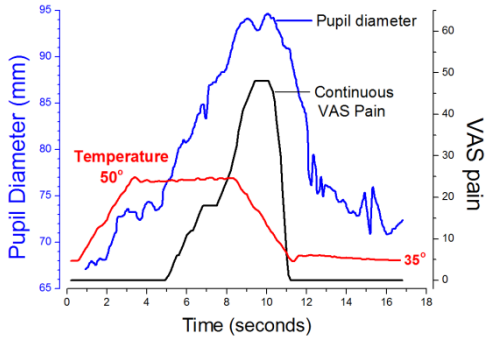

Figure 2: Time course of heat stimulus and of VAS and pupil responses

We next examined the relationship between pupil response and pain report as a function of affective distress. We estimated affective distress as the sum of scores to the pain catastrophizing scale, the CSED depression scale, the state trait anxiety inventory, and the pain anxiety symptom scale and linearly regressed this on pain report. The residual from the regression line for each individual was related to baseline pupil diameter as a measure of tonic LC activity. Despite there being a very small range of affective distress in this largely normal population, the residual (tendency to adhere to cognitive-affective state in pain reporting) was significantly related to baseline pupil diameter (Figure 3).

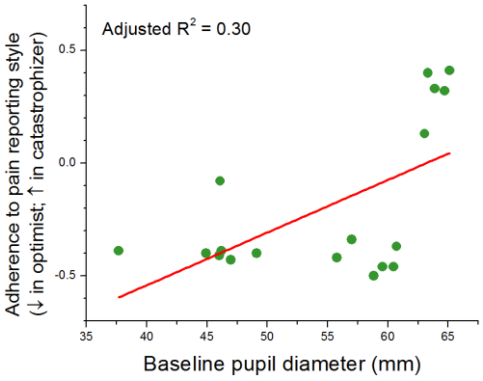

Figure 3: Relationship between resting pupil diameter and pain reporting by affective distress

Expectations alter pain experience. We are also manipulating expectations in this study of healthy volunteers. Pain stimuli are first presented as a random series without cues, then as a series preceded by 6 sec with an auditory cue to indicate whether the stimulus would be mildly (47^0C) or moderately (50^0C) painful, then as a series with 20% of the cues incorrect. So far we have observed a mild, but highly significant reduction in pain from random to cued condition, consistent with a recent report on the role of uncertainty in pain reporting (Yoshida, 2013). During miscuing, there was a greater effect of negative expectations (expect less pain) than positive ones (expect more pain), as previously reported (Koyama, 2005). In the proposed

study we gather feasibility data in a clinical population (patients with moderate osteoarthritis of the hip or knee) to test whether we can manipulate expectations on pain in this population.

Gabapentin and modafinil to increase LC activity and gain. In animals and humans, the alertness enhancing drug, modafinil (Provigil™) increases tonic LC activity and increases pupil diameter. Although large doses of this drug (800 mg) can increase blood pressure and heart rate, this has not been observed in these studies of over 100 people who received 200 mg (Hou, 2005; Nikolaou, 2008; Minzenberg, 2008; Schmaal, 2013; Geng, 2013). For this reason, we will examine the effects of modafinil, 200 mg, on pupil diameter and its effect to alter pain reporting as a function of baseline state by increasing gain.

A more relevant drug to the question of chronic pain after surgery is gabapentin, and some clinical trials have suggested that perioperative treatment of this drug can reduce the incidence of this problem (Schmidt, 2013). In the NIH application we propose to test gabapentin rather than modafinil because our previous work with direct measures in rats and cerebrospinal fluid norepinephrine sampling in humans is consistent with gabapentin activating LC in both species (Hayashida, 2007). The pupil measurements in this feasibility study will more directly assess whether gabapentin does indeed increase LC activity in humans. Should it fail to demonstrate a reasonable effect size to dilate the pupil, we will revise the NIH application to study modafinil rather than gabapentin. As such, these preliminary data are very important to the design of the final study.

Study Design.

Hypotheses: (1) Gabapentin and modafinil will increase resting pupil diameter with a moderate effect size in patients with osteoarthritis; (2) Expectations will modify pain experience with a moderate effect size in these patients

Study design: Single-center, randomized, controlled study of gabapentin, modafinil, and placebo in 30 subjects (10 per group) with moderate osteoarthritis pain of the hip or knee or healthy individuals without pain

Primary outcome measures: (1) Resting pupil diameter and response to noxious stimuli after study drug; (2) Interaction between resting pupil diameter and correlation of cognitive-affective state to pain reporting.

Inclusion criteria: Adult, nonpregnant adults scheduled with moderate pain (verbal score of ≥ 4 ≤ 7 on 0-10 scale for average pain intensity with normal activity) from osteoarthritis of the knee or hip, or healthy individuals without pain, American Society of Anesthesiologists physical status 1-3, able and willing to perform the study procedures, including sitting in a chair for 45 min. Individuals must be able to read.

Exclusion criteria. (1) Inability to complete questionnaires; (2) Pregnancy; (3) Currently taking gabapentin or > 50 mg morphine equivalents/day; (4) advanced or unstable cardiac, pulmonary, renal or hepatic dysfunction; (5) history of previous eye surgery; (6) psychotic disorder or a recent psychiatric hospitalization.

Catastrophizing-Optimism continuum assessment. Prior to the initiation of experimental procedures, each participant will be administered the battery of questionnaires Table 1. From these questionnaires, we will place each participant on a dimensional continuum that describes their general cognitive style. We will use multidimensional scaling (MDS) to force catastrophizing and optimism as 2 ends of this continuum (Figure 4). These two constructs

describe cognitive styles that are strongly inversely associated with each other; MDS will provide the optimal weights to best order individuals on this latent scale. Studies have examined the interplay of these constructs with other psychological concepts such as acceptance, pain-related disability and psychosocial adjustment and have found that both are reliably associated with the positive and negative aspects of the adjustment to pain.

Table 1. Questionnaires
Stanford Expectations of Therapy Scale
WOMAC- Osteoarthritis Index
Life Orientation Test-Revised (LOT-R)
PROMIS- Depression
PROMIS- Anxiety
Pain Medication Attitudes Questionnaire (PMAQ)
Pain Locus of Control Scale (PLOC)
Pain Self-Efficacy Scale (PSE)
Barratt Impulsivity Test
Fear of Pain Questionnaire
Pain Catastrophizing Scale (PCS)
Tampa Scale of Kinesiophobia (TSK)

Study procedures: A total of 30 subjects with moderate average daily pain from osteoarthritis of the knee or hip or subjects with no pain will be recruited and will come to the clinical research unit at Wake Forest. Informed consent will be confirmed and they will complete the questionnaires. We will take a verbal medical and medication history and obtain blood pressure and heart rate measurements. Verbal pain intensity report (0-10 from no pain to worst pain imaginable) will be obtained from 5 sec heat stimuli, separated by 30 sec, delivered to a nonpainful area of skin on the arm as described in preliminary data. During pain testing, study subjects will sit in a comfortable chair in a low-ambient light room with their head positioned on a chinrest for continuous recording of pupil diameter using a near infrared recording system as described in preliminary data. Pupil diameter and probe temperature will be passed through an analog to digital converter and acquired at 60 Hz for subsequent analysis.

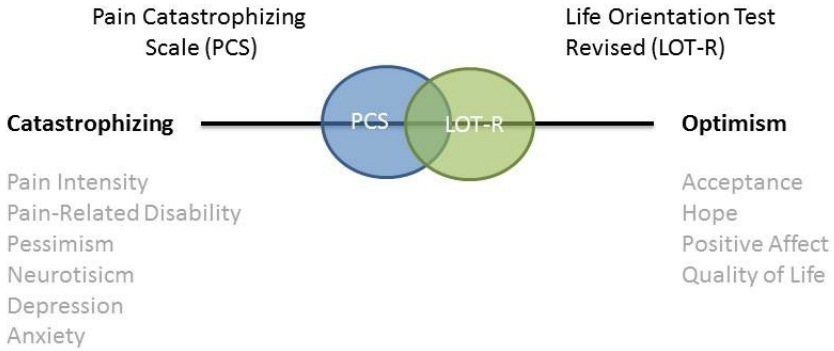

Figure 4: The dimensional structure of the continuum of cognitive style to be used, including psychosocial constructs associated with each end.

Five sequences of test stimuli will be presented, with a brief break in between each sequence (Figure 5A). The first sequence will consist of 7 stimuli, from 39^0 to 51^0 C in 2^0C increments, in ascending order. Data from this training sequence will not be used for analysis. Sequences 2 and 3 will consist of 5, 5-sec stimuli, presented in random order, to generate moderate (50^0C) and mild (47^0C) pain (random condition). Sequences 4 and 5 will also consist of random presentation of 5 stimuli at these temperatures, but with different auditory tones 6 s prior to stimulus onset to correctly cue the stimulus temperature (cued condition).

Subjects will then be randomized to receive oral gabapentin, 900 mg, modafinil, 200 mg, or placebo, followed 2 hr later by pain testing with pupillometry, consisting of different sequences (Figure 5B). The random and cued paradigms will be presented twice each (only 1 representative shown in Figure 5B), followed by a sequence with one miscue in the positive expectation for pain direction (signal for 50^0C but deliver 47^0C) and one in the negative

expectation for pain direction (mistrust condition, yellow bars in Figure 5B). Subjects will provide verbal pain intensity scores after each stimulus.
The pre-drug and post-drug set of sequences will take approximately 30-40 min including breaks between sequences of stimuli. Following this subjects will be discharged from the clinical research unit accompanied by a responsible adult.

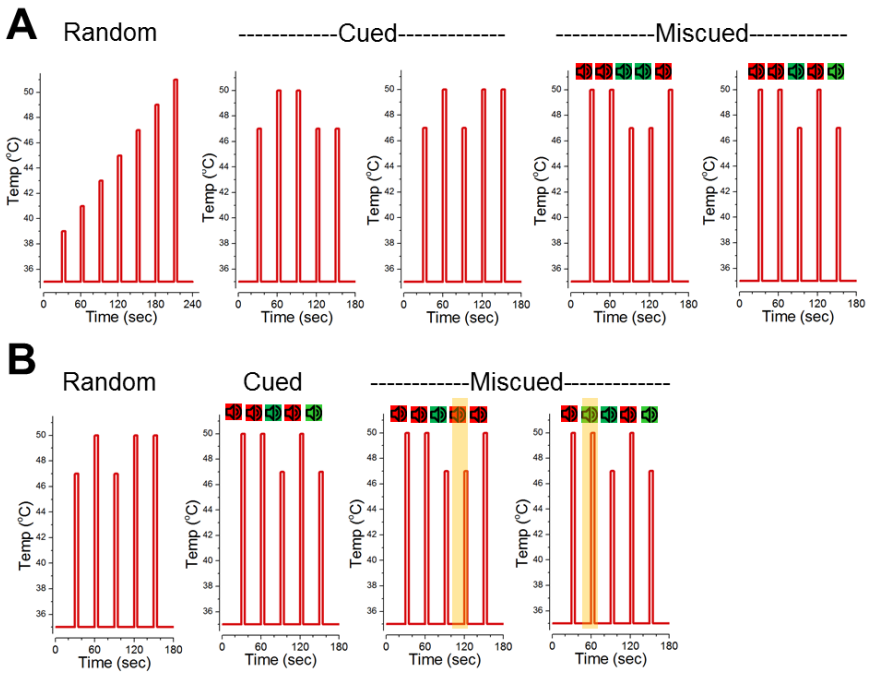

Figure 5: Heat stimuli give before (**A**) or after (**B**) study drug

Subject payment. Subjects will be paid $250 for participation in the study.

Data analysis. Pupil diameter data will be conditioned to remove blink and saccade artifacts and smoothed using an autoregressive filter. The local resting diameter will be determined representing the average smoothed value for the 500 msec preceding the stimulus onset. The pupil response to each stimulus is calculated as the mean pupil diameter during the 5 sec stimulus after accounting for lag time from onset of stimulus to onset of pupil response and is expressed as a % change from the local resting diameter (see our preliminary data for examples). Multidimensional Scaling (MDS) will be used to create a single dimensional scale from the catastrophizing and optimism scores (i.e., responses from these two questionnaires will be weighted and scaled to create a single-dimensional construct)

To determine the interaction among the factors of interest, and to accommodate the many repeated measures within each participant, we will utilize Generalized Estimating Equations. In our experience, the pupil response to painful stimuli is well modeled by a normal distribution with an identity link and an AR1 repeated measures covariance structure. To examine our hypotheses, we will model percent pupil change (the DV) using fixed effects for stimulus temperature, catastrophizing-optimism score (i.e., cognitive-affective state), and pre-stimulus baseline pupil diameter (i.e., LC activity). The association between cognitive-affective state and pain reporting will first be examined, and in a later block the moderating effect of baseline pupil size will be entered.

The goal of this feasibility study is to estimate the effect size of drugs on pupil diameter and the strength of interaction between pupil diameter and the relationship between cognitive-affective state.

Expected results. We anticipate, based on preliminary data, that pain reporting will be weakly correlated with cognitive-affective state and that resting pupil diameter as a reporter of LC gain will interact with this correlation or tendency to apply cognitive style to pain reporting. We anticipate overall reduced pain reporting after placebo (placebo effect) and that the magnitude of this reduction and that of negative of pain will be inversely related to location on the optimism-catastrophizing continuum (i.e., greater placebo effect, greater effect of negative expectations of pain, and lesser effect of positive expectations of pain in strong optimists). After gabapentin or modafinil we anticipate that resting pupil diameter will be greater (i.e. greater tonic LC activity) than placebo. According to the gain concept, the effect of gabapentin on pain reporting across conditions should depend on cognitive-affective state, with overall reductions in pain reporting in strong optimists and amplification of pain in strong catastrophizers. The study is not powered to definitively show the effects of these drugs on either pupil diameter or its relationship to pain reporting as a function of optimism-catastrophizing. Rather, it is to provide feasibility, effect size, and variability data to support the choice of drug and power analysis for the eventual controlled study.

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