Official Title: A Multi-Center Study: Predicting, Understanding and Speeding Recovery after Total Joint Replacement

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Background, Rationale and Context

Chronic pain after surgery is typically defined as pain outlasting the normal healing process from uncomplicated surgery, usually 2-6 months. Given over 250 million major surgical procedures performed annually on a global basis and an incidence of chronic pain after surgery of 10-50% (Kehlet, 2006), the problem of chronic pain after surgery is clearly a major public health problem. Major surgery also results in acute physical disability which is especially important after procedures for which the primary indication is to improve or remove disability, exemplified by major total joint replacement surgery. We chose to study total knee arthroplasty (TKA) and total hip arthroplasty (THA) in this NIH grant application for two reasons. *First,* TKA is a commonly performed surgery to reduce pain and improve function, and 3.5 million TKAs are predicted to be performed each year in the US by 2030 (Kurtz, 2007). *Second,* although most patients show improved joint range of motion from this surgery, approximately 40% of patients fail to improve function after TKA as assessed by validated measures of minimally clinical important improvement (MCII), and 10-20% are left with chronic, moderate to severe pain (Maxwell, 2014; Singh, 2014a).

Critical barriers to progress addressed by this study. These are fourfold:

1. Focus on dichotomous outcomes. Clinical and preclinical studies on recovery from surgery utilize dichotomous outcomes, which makes no biological sense. Recovery after injury is a dynamic process, and the very few longitudinal, prospective studies in this area show that the incidence of this dichotomous outcome continues to decline for years following surgery (Kaasa, 2010).Thus, choosing an arbitrary time to define chronic pain or disability after surgery tells us little about the path upon which patient are recovering and when they will recover. The cartoon in Figure 1 depicts the problem. The incidence of "chronic" pain or disability changes over time and predictive models based on disparate times are likely to be inconsistent and potentially misleading. The subject in orange in Figure 1, for example, experienced considerably more pain, disability, and possible risk for opioid misuse, than the one in blue, but both are lumped as "no chronic pain" at 12 months. We do not argue that dichotomous outcomes at fixed times after surgery are worthless as primary outcome measures for interventional trials, but beyond this we believe they represent barriers to understanding and progress.

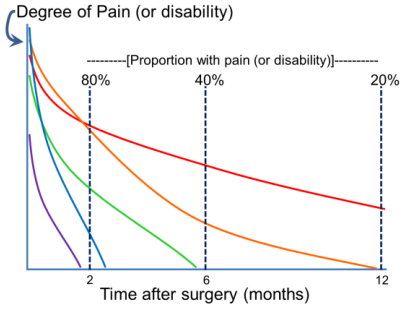


Figure 1: Time course of recovery from pain or disability in 5 hypothetical patients after surgery

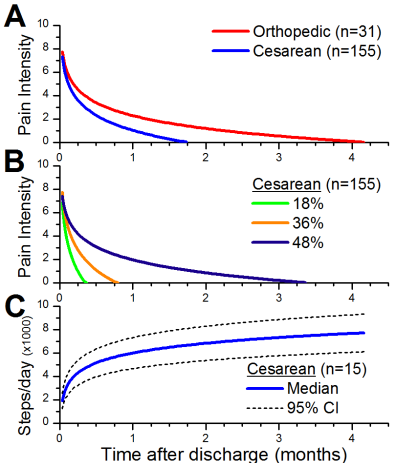


Figure 2: **A)** Modeled time course of recovery from pain, **B)** latent classes of recovery, **C)** and time course for recovery in activity

Clearer definition of normal time course of improvement in pain and other patient-centered aspects of recovery could significantly impact surgical decisions regarding candidates for surgery and managing expectations (Losina, 2012). Previous efforts to define trajectory of recovery from pain and disability were limited to a few days after surgery (Brewer, 2007; Chapman, 2011; Althaus, 2014), although one study recently extended this to 45 days (Gaudilliere, 2014). To demonstrate feasibility of high density time sampling for

months after surgery we recorded frequent pain assessments in 31 patients after lower extremity total joint arthroplasty and 155 women after cesarean delivery. The time course of daily pain intensity was best modeled to a log of time function in both cases and, as expected, worst daily pain was initially slightly less intense and resolved considerably more rapidly after cesarean delivery than arthroplasty (Figure 2A). Latent class analysis of the cesarean delivery group yielded 3 distinct patterns of recovery (Figure 2B), although this is an ongoing study and 550 total subjects will be required to allow adequate power for a stable latent class analysis.

2. Focus on pain in isolation. Major surgery induces dysfunction in many patient centered domains, including pain, physical disability, cognitive dysfunction, and risk of prescription opioid misuse, which has been linked to impulsivity (Marino, 2013). For many surgical procedures, and certainly for TKA, patients choose surgery in the hope of less pain and better quality of life. Yet most studies focus on one or at most two outcomes, most commonly components rather than integrated patient centered outcomes. We will repeatedly apply the simple, 12-question World Health Organization Disability Assessment (WHODAS) 2.0, recently validated in postoperative patients to define disability-free survival (Shulman, 2015) in order to define the trajectory of this patient-centered, integrated outcome. We will also frequently quantify the important components of pain (feasibility shown in Figure 2A and B) and physical activity using Fitbit™ accelerometers (feasibility shown in Figure 2C) in order to define trajectory of recovery in these domains. We will also repeatedly assess executive function and impulsivity (along with daily opioid use) to test novel hypotheses in parallel with lab projects in this NIH Program Project (P01) application which assess these constructs. Finally, we will examine the associations previously shown using dichotomous outcomes between known risk factors for individuals with chronic pain and dysfunction after surgery (Scott, 2010; Wylde, 2011; Rakel, 2012; Singh, 2014b) but applying growth curve analysis of recovery in pain, physical activity, and disability free survival.

3. Lack of unifying testable hypothesis. Most critically, the field lacks a testable, mechanistic and actionable hypothesis of mechanisms of recovery from these impairments after surgery. We provide one:

Central hypothesis: Activity of the locus coeruleus (LC) at the time of and in response to surgical injury is a key determinant of speed of recovery across pain and other patient-centered domains.

The LC provides exclusive or near-exclusive innervation to the cortex, spinal cord, and several midbrain regions, where it provides important moderating input to areas involved in (among other things) pain, fear, attention, and impulsivity. LC neurons exhibit two modes of activity: spontaneous, tonic, low frequency firing (0.1-5 Hz) and phasic bursts (10-25 Hz) in response to external, sensory or cortical network stimuli.

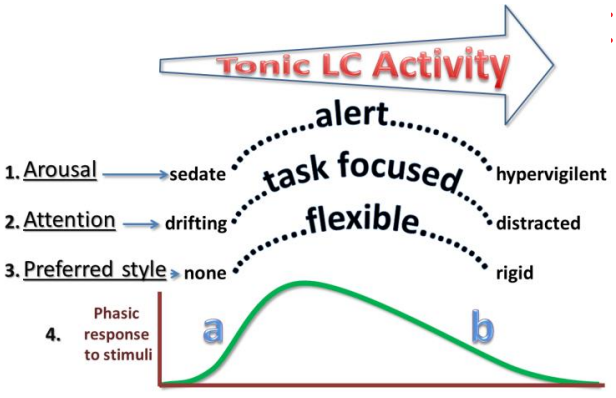


Figure 3: Conceptual relationship between tonic activity and level of arousal, attention, application of preferred cognitive style, and phasic response to stimuli. For domains 1-3 the curved text is meant to show an inverted U effect on these aspects of cognition. Drugs which increase tonic LC activity may exert opposite effects, depending on level of tonic activity (↑ if in a and ↓ if in b).

Two aspects of LC function determine its widespread modulatory effects. First, the interplay between tonic and phasic LC activity determines how the LC molds responses to the environment (Figure 3). At low to moderate levels of tonic norepinephrine (NE) release from LC afferents, stimulation of α2-adrenoceptors increases gain across cortical circuits. 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, as recently demonstrated by fMRI in humans engaged in learning tasks (Eldar, 2013). As tonic LC activity increases, so does level of alertness and the ability to focus on task (Figure 3, domains 1 and 2) accompanied by the tendency to exploit the environment, which is viewed as predictable. With higher tonic NE release, such as occurs under acute stress, these effects are degraded by activation of lower affinity α1- and β-adrenoceptors, resulting in hypervigilance, distraction (Suto, 2014), and tendency to explore the environment which is viewed as surprising / unpredictable (Gilzenrat, 2010; Jepma, 2011). Project 2 (a laboratory project in the P01 application) induces high tonic LC activity to test whether this results in beneficial effects to reduce impulsivity or detrimental effects to exaggerate attention deficits, and we will assess in humans the effect of tonic LC activity on these parameters following TKA. Impulsivity and attention are specifically regulated by the locus coeruleus, are relevant to postoperative cognitive dysfunction and potential opioid misuse, and are being studied in the preclinical arms of this NIH program project grant.

Domains 3 and 4 are particularly relevant to pain. For all but the lowest range of frequencies, increases in tonic LC neural firing frequency are accompanied by decreases in phasic bursts in response to salient stimuli (Figure 4A). Project 1 (a laboratory project in the P01 application) shows in rats that a manipulation which increases tonic LC activity reduces release of NE in the spinal cord in response to a noxious stimulus and reduces Conditioned Pain Modulation (CPM), a form of endogenous analgesia (Figure 4B). In preliminary data, we observed that strength of CPM in 7 healthy volunteers (conditioning stimulus of foot in cool water with test stimulus of 5 sec 49^{0}C stimulus to forearm (Nahman-Averbuch, 2013)) was inversely related to resting pupil diameter in a constant luminosity, darkened environment as a proxy for tonic LC activity (Figure 4C). In animals, CPM is dependent on LC→spinal noradrenergic signaling, and in both animals and humans, low CPM is associated with a greater risk of chronic pain after surgery (Yarnitsky, 2008; Peters, 2015). We will therefore test the hypothesis that resting pupil diameter, a stable trait in humans for long periods of time (Alnaes, 2014), predicts the strength of CPM and partially regulates the speed of recovery from pain after surgery.

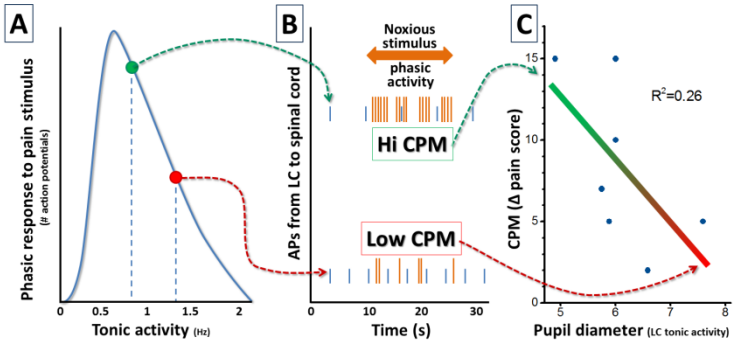


Figure 4: **A)** In this example an individual with higher tonic LC activity (Red) has less phasic response to a noxious stimulus than one with lower tonic activity (Green). **B)** This yields fewer noxious stimulus-induced action potentials (APs) of LC neurons with spinal projections (orange bars) resulting in lower CPM. **C)** As predicted by this hypothesis, CPM strength in 7 subjects was inversely related to resting pupil diameter, a validated measure of tonic LC activity in humans.

According to our central hypothesis, LC activity does not just regulate the time course of spinal sensitization and ascending nociceptive input, it also alters the pain experience, which results from supraspinal processing of this bottom-up signal (Figure 3, domain 3). In humans, increased tonic LC activity results in stronger reliance on an individual's preferred visual or semantic learning style (Eldar, 2013). To test whether a similar relationship exists in response to pain, 16 individuals with osteoarthritis of the hip or knee answered a series of questionnaires to place them on a catastrophizing↔optimism (C↔O) cognitive continuum, and resting pupil diameter was measured to infer tonic LC activity. Noxious heat stimuli were applied to the forearm using a Peltier-controlled thermode in 5-sec pulses, ranging from innocuous (41^{0}C) to mildly or moderately noxious (47^{0}C and 50^{0}C, respectively). A generalized estimating equation (GEE) analysis was applied to examine the repeated measurements of

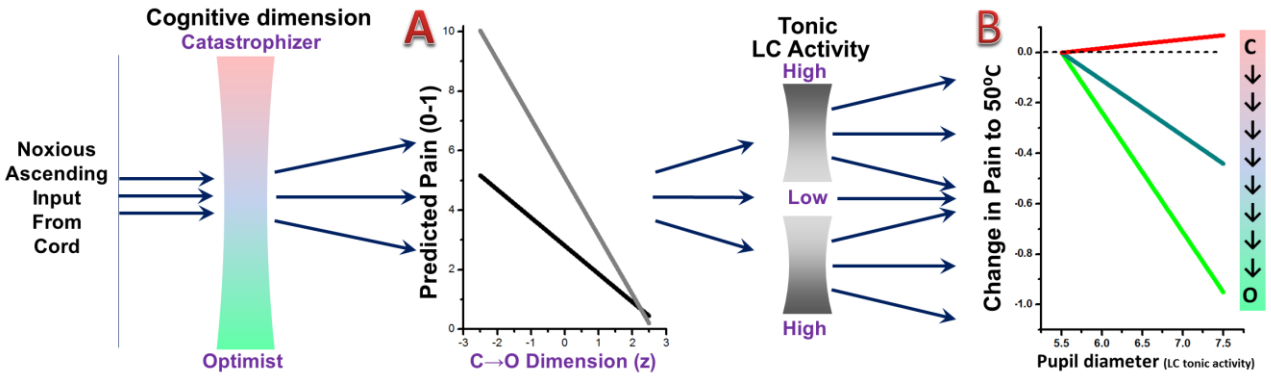


Figure 5. Ascending input from the spinal cord is conceptually filtered through a cognitive dimension which disperses pain experience, as supported by **A)** an observed relationship between predicted pain and preferred style on this C↔O dimension. We hypothesize that further dispersion of pain occurs through filtering depending on degree of tonic LC activity, as supported by **B)** Spread of pain dependent on C↔O dimension increases as tonic LC activity (inferred by pupil diameter) increases (n=16 osteoarthritis patients).

temperature condition on C↔O dimension, and resting pupil diameter on pain reporting. We anticipated that pain report would be affected by preferred style on the C↔O dimension, and this was observed at both 50^0 and 47^0 stimuli (Figure 5A; p=0.0007). We anticipated that additional variance in pain report could be identified by the interaction between C↔O style and resting pupil diameter, and this was also observed (Figure 5B) although not significant in this underpowered small pilot sample. As resting pupil diameter increased, pain report tended to increase or decrease depending on preferred style in the C↔O dimension. These data are consistent with tonic LC activity in this population residing in area **b** of Figure 3, since increased tonic activity increased rigidity to apply the preferred style. Tonic LC activity and hence this relationship may differ in the surgical population.

This complex interaction between tonic LC activity and C↔O style on recovery from pain after surgery is important because its determinants (resting pupil diameter and cognitive assessment) can be easily measured and because it provides novel and testable predictions in the laboratory and clinic. These preliminary data strongly support the use of pupillometry to infer tonic LC activity, as they also support the central hypothesis and the feasibility of testing it.

4. Inability to target treatment to responders. There are two critical barriers to identifying and targeting treatments to speed recovery from surgical injury. *First,* surgical procedures utilized to study pain in rodents result in recovery within a few days (incision model of (Brennan, 1996)), or no recovery over many months (e.g., spinal nerve ligation (SNL) model of (Kim, 1992)). This P01 application utilizes partial SNL (Guan, 2010), a surgical procedure which resolves over 2 months, with recovery delayed if a negative affective phenotype is induced prior to injury. *Second*, treatments based on theory or studies in rodents have been largely negative in the clinic, including prolonged regional blockade, gabapentinoids, clonidine, ketamine, and serotonin-NE reuptake inhibitors (SNRIs).
This may reflect inability to identify responders.

Without a testable and mechanistic rationale for treatment, understanding treatment failure and prospectively identifying responders are difficult. This proposal will build on our central hypothesis, that the interaction between tonic LC activity and C↔O style regulates speed of recovery, to test whether responders to a drug which increases tonic LC activity can be predicted. We chose gabapentin as that drug, based on animal and novel preliminary data in humans. The osteoarthritis subjects described in Figure 4 were randomized to receive oral

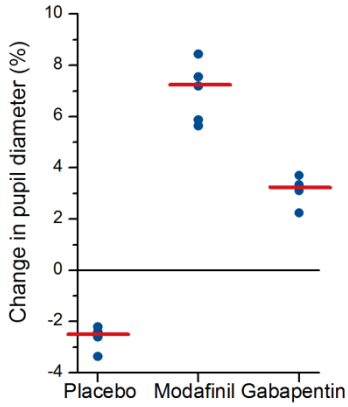


Figure 6: Change in pupil diameter 2 hr after oral treatment (bars are median)

modafinil, a drug known to increase tonic LC activity and pupil diameter (Minzenberg, 2008), gabapentin, 1200 mg, or placebo. Two hr later, pupil diameter increased after gabapentin and modafinil in comparison to placebo (Figure 6), consistent with an increase in LC activity from gabapentin in rodents (Hayashida, 2008) and in CSF NE in patients receiving gabapentin (Hayashida, 2007). The proposed clinical study will test high-order interactions between pupil diameter, C↔O dimension and drug on speed of recovery from pain after TKA. If positive, this would explain the failure of gabapentin to exert large effects to reduce pain presence months after surgery in a general population and provide a testable algorithm to use simple patient characteristics – resting tonic LC activity as measured by pupillometry and C↔O style as measured by simple questionnaires – to those who may be most helped or most harmed by this drug. An example of a tool using minimum effect sizes observable in the proposed clinical study is available at https://pain.shinyapps.io/clinicalPredictions/ (adjacent screenshot). This tool assumes an inverted U effect of resting pupil diameter on speed of decline in noxious ascending input from the spinal cord and that of reliance on preferred style in the C↔O dimension. The effect of gabapentin, which increases tonic LC activity, on speed of recovery will depend on both pre-drug pupil size and cognitive style in the C↔O dimension.

In summary, the significance of the proposed work lies in **1)** shifting dichotomous, static measures to continuous primary outcomes in recovery from surgery; **2)** investigating several key, patient-centered domains rather than just pain intensity in recovery; **3)** providing a mechanistic hypothesis linking tonic LC activity and its interaction with C↔O style to speed of recovery across these domains; and **4)** testing this hypothesis using a commonly applied therapeutic intervention to generate novel, clinically actionable results.

Objectives

We propose a two-site, longitudinal, randomized clinical intervention study to examine three specific aims:

Aim 1: Characterize the dynamic pain experience, activity, and cognitive response after TKA or THA and determine patterns of recovery in these domains

Aim 2: Test whether gabapentin alters time course of recovery after TKA or THA in a manner dependent on its interaction with pre-drug pupil diameter and preferred style in the C↔O dimension

Primary Hypothesis: Novel variance beyond established associations in recovery from pain following TKA or THA surgery is accounted for by the interaction between pupil diameter and C-A state, and this interaction predicts efficacy of gabapentin to speed recovery.

Key secondary hypotheses: Disability, impulsivity, and attentional deficits recover after TKA or THA surgery follow a log of time pattern, and are predicted by C-A state and its interaction with pupil diameter. Gabapentin increases resting pupil diameter in patients scheduled for TKA or THA who are receiving high doses of opioids

Methods and Measures

Primary analysis: Three way Resting Pupil Diameter*C-A State*Drug treatment in the 250 subjects not on high dose opioids.

Setting

Subjects recruited at Wake Forest Baptist Medical Center will be identified by research personnel in the Departments of Anesthesiology and Orthopaedics. Research personnel will approach the subjects while they are in a private exam room, the study will be explained to the subject and the subject will be given a copy of the study consent form to read. Informed consent may be obtained at this time or the subject may choose to take the informed consent home and call the study personnel to schedule an appointment to come to the Headache and Pain Research Unit (HPRU) for consent and their initial study visit. Subjects will be seen in the HPRU (subjects may choose to have their 2 month and 6 month postoperative study visit occur in conjunction with their postoperative visit to their surgeon at Davie Medical Center) for 3 study visits; approximately 2 weeks prior to surgery, approximately 8 weeks after surgery and 6 months after surgery.

Subjects will also be recruited at the Cleveland Clinic in Cleveland, Ohio under the direction of Dr. Daniel Sessler, Professor and Chair, Cleveland Clinic Lerner College of Medicine.

Subjects selection criteria

We will recruit patients having primary, unilateral total knee arthroplasty (TKA) or unilateral total hip arthroplasty (THA).
We will recruit 300 subjects in primary analysis - taking < 100 mg morphine equivalents/day (low dose opioid) to test gabapentin's effect on pupil diameter – taking >100 mg morphine equivalents/day (high dose opioid).

- **Inclusion Criteria**
  Adult, non-pregnant adults scheduled for elective total knee replacement, American Society of Anesthesiologists physical status 1-3, able and willing to perform the study procedures. Individuals must be able to read and write English and have a stable residence.

- **Exclusion Criteria**
  (1) Inability to complete questionnaires; (2) Pregnancy; (3) Litigation or workers compensation related to their joint surgery; (4) history of Raynaud's disease of the feet; (5) suffering from a psychotic disorder or a recent psychiatric hospitalization; (6) history of eye surgery or topical eye medications that would render pupillometry unreliable or would directly affect pupil diameter; (7) any disorder that would affect pupil responsivity or prevent accuracy of pupillometry such as movement disorders. (8) Exclusion for preoperative calculated GFR <30 ml/min, hold of study med if postop GFR<30 ml/min. (9) severe Chronic Obstructive Pulmonary Disease (COPD) requiring home oxygen. (10) Obstructive Sleep Apnea (OSA) with daily use of CPAP at home.

- **Sample Size**
  Two-center interventional study of 300 evaluable patients having primary, unilateral TKA or unilateral THA at Wake Forest School of Medicine and Cleveland Clinic. Patients will be stratified by norepinephrine serotonin reuptake inhibitor (NSRI) use, 300 subjects not on high dose opioids will be included in the primary analysis to test the effect of gabapentin on resting pupil diameter.

Interventions and Interactions

Preoperative procedures. Eligible subjects will be identified at least 3 weeks prior to surgery, informed consent obtained, and a ~ 2hr preoperative assessment will be performed, consisting of 3 parts. We will record demographic and history information, including pre-existing pain elsewhere, female subjects of child-bearing potential will have a urine pregnancy test performed.

In the first part we will administer thermal heat temperatures ranging from warm but not painful to painfully hot. We will ask subjects to indicate when they feel warmth or pain, and to rate the pain using a scale from 0-10.

The second part will consist of subjects to completing a series of 3 questionnaires on the computer, 2 questionnaires on paper, and play 2 simple card games.

The third part will consist of the subject experiencing the warm and hot temperatures again while we make a recording of their pupils.

We will administer questionnaire-based measures of psychological state, physical function, and pain (Table 1). Questionnaire responses will be entered via a custom designed REDCap data entry form and checked for completeness by the data coordinating center. We will have the subjects complete 2 of the questionnaires (PLOC and PSE) on paper the evening before the visit as well as the PAS and DSI. The LOT-R, PCS, and WOMAC will be completed on the computer during the first visit. The remaining questionnaires will be completed at home and returned to the study team on the day of surgery (Stanford Expectations of Therapy Scale, PROMIS-Depression, PROMIS-Anxiety, PMAQ, Barratt Impulsivity, Fear of Pain, TSK, WHODAS 2.0, BRS)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 7). These questionnaires will assess activities of daily living and associated disabilities.

Upon review of the questionnaire data, the study staff will notify the primary attending surgeon for any subject showing suicidal ideation as well as the study staff will call the subject and inform them.

The Daily Stress Inventory (DSI) and the Perceived Arousal Scale (PAS) will be completed the night before the scheduled appointment and the PAS will be completed once during the scheduled appointment. The Modified Pain DETECT will also be completed during visit 1.

Table 1. Preoperative Questionnaire

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)
WHO Disability Assessment (WHODAS 2.0)
Brief Resiliency Scale (BRS)
Modified Pain DETECT
Daily Stress Inventory (DSI)
Perceived Arousal Scale (PAS)

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.

We will perform pupillometry during presentation of calibrated noxious stimuli. Subjects will report pain and unpleasantness using mechanical 10 cm visual analog scales (VAS) to 5 sec duration heat stimuli (37^0 to 50^0 C in 2^0 increments) applied to a 2 cm2 area of skin on the forearm using Peltier-controlled thermode (TSA-II®, Medoc, Ramat Yishai, Israel). Stimuli will be separated by 30 sec and the all temperatures will be presented in an ascending series for training followed by a random series to generate a stimulus response as previously described (Hood, 1995; Eisenach, 2010). We will deliver 3 blocks of thermal stimuli to each subject for the pupillometry session. The blocks will include the same temperatures (37^0C; warm threshold, 46^0C; pain threshold and 50^0C; painful stimuli) delivered 3 times each per block. Each block will consist of a random presentation of these temperatures. We will provide verbal instructions to the subjects immediately prior to the block: block 1 will be labeled as ½ of the stimuli will be painful and ½ of the stimuli will not be painful, block 2 will be labeled as 80% of the stimuli will be painful and block 3 will be labeled as 20% of the stimuli will be painful. The thermal probe will be moved to a different area of skin on the forearm for each testing sequence. The debriefing statement is included in Appendix 3.

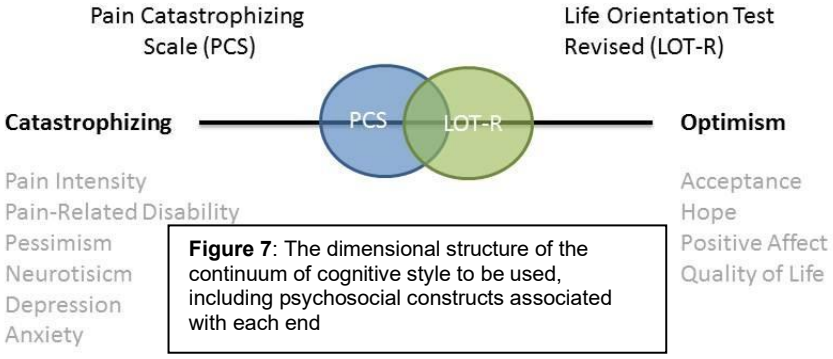


Figure 7: The dimensional structure of the continuum of cognitive style to be used, including psychosocial constructs associated with each end

We will then test CPM as previously described (Nahman-Averbuch, 2013) by recording VAS pain and unpleasantness from a 5 sec, 49^0C stimulus on the volar forearm before, 30 sec after insertion of the foot of the extremity not planned for operation in 10^0C water, the foot will remain in the water for a total of 90 seconds. 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 and acquired at 60Hz for subsequent analysis.

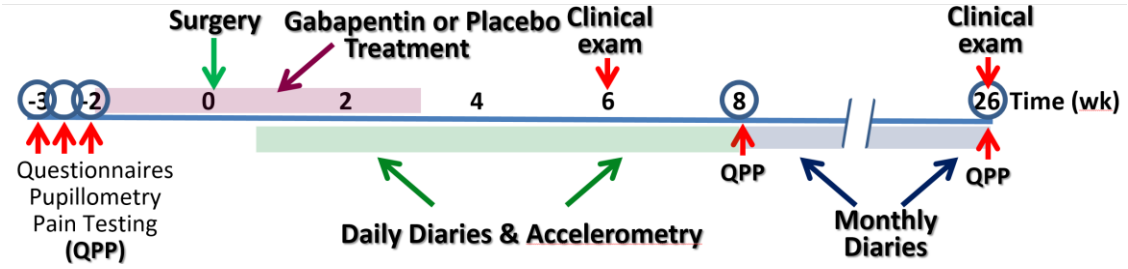
We will have the subjects wear a portable heart monitor during the study visit so that the researchers can record the heart rate to assess the state of arousal to coincide with the PAS questionnaire that will be completed. The heart rate monitor will be a non-invasive monitor.

Subjects will be trained and provided with a tablet device for daily diary entries and the accelerometer. The accelerometer has wireless connectivity such that daily diary and activity will be time stamped and can be easily uploaded by the patient to the data coordinating center on a regular basis. We will utilize a password protected web based database tool for near real-time access to facilitate adherence (e.g., phone calls or emails when participants fail to wear the device during regularly scheduled time points).

We will have subjects begin using the tablet and wearing the accelerometer 2 weeks prior to surgery so that they will become familiar with the devices to increase compliance and adherence to the protocol after surgery.

The tablet will also have the capabilities to access PEBL software for cognitive assessment. This open-source software employs several cognitive tasks that look and feel like challenging games that allow the assessment of different areas of cognitive function. The specific tasks will be the Iowa Gambling Task to assess impulsivity. The Wisconsin Card Sorting Task will be utilized to assess executive function. Participants will complete these tasks at baseline and again at several times after hospital discharge (Figure 8).

Figure 8: Timeline of study. Cognitive tasks are performed at circled times.



Drug treatment. Patients will be randomized, stratifying for NSRI use, to equal number to receive gabapentin of placebo pills formulated by the research pharmacy at the institutions. Drug treatment will begin 2 weeks prior to surgery and continue 3 weeks afterwards. To reduce treatment-limiting side effects subjects randomized to gabapentin will receive 900 mg/day for the first week, 1800 mg/day for the next 3 weeks, and 900 mg/day for the last week (Figure 8). Subjects will be contacted 5 days after beginning the 1800 mg dose and assessed for bothersome side effects (sleepiness, dizziness, confusion) that are interfering with normal activities of daily living(ADL's). If bothersome side effects are present at this time dose will be decreased back to 900mg/day. Subjects' will receive a weekly phone call while on study drug treatment and assessed for side effects, difficulty breathing or falls that have occurred.

Intraoperative and in-hospital care. We will not limit intraoperative surgical or anesthetic management or in-hospital analgesic management. A study team member will record potential confounds including surgical complications, in-hospital physical therapy, intraoperative and postoperative opioid, gabapentin, ketamine, and regional anesthesia administration, and days from surgery to discharge. For patients receiving a spinal injection as part of clinical care, we will collect a 2 ml CSF sample for planned exploratory analyses for measures of noradrenergic activity (norepinephrine) and chronic stress state (NPY, cortisol, IL-1β). Research staff will see the subject daily in the hospital to have them complete the daily diary questions. Study medication will be held during hospitalization if postoperatively the calculated GFR<30 ml/min until resolution of lab abnormality.

Post-hospital discharge measures. Patients will begin daily evening electronic diary entries on the day of hospital discharge for 8 weeks then once monthly (beginning 3 months after surgery) study staff will call the subject to collect the diary questions until 6 months after surgery. Patients will also answer a weekly WHODAS 2.0 (12 questions) on the electronic diary and will complete this monthly during their phone call as well. These assessments will typically take less than 2 minutes and assess IMMPACT recommended domains (Turk, 2006): pain intensity, physical functioning, emotional functioning, and participant ratings of global improvement and associated symptoms. Electronic diary entries are captured wirelessly using the participant's home wireless connection via the customized secure electronic, password protected database. Both sites will be provided with several tablets that are equipped with pre-paid 4G wireless access to ensure that participants without home Internet connections can participate. The diaries will be monitored and maintained by the data coordinating center in real-time; if a participant misses a diary entry, they will be emailed or called (their preference) to ensure maximal adherence to the protocol. Using these procedures we have been able to obtain > 95% adherence in our previous diary studies. Participants will also wear the accelerometer for the first 8 weeks after discharge. Participants will also complete the cognitive tasks (Iowa Gambling Task, Wisconsin Card Sort,) that they were introduced to at the baseline session at, 2 months, and 6 months after hospital discharge. The Iowa Gambling Task will again be administered via the PEBL software. Questionnaires done at pre-randomization (Table 2) will be repeated at 2 and 6 months after surgery. Finally, we will also record objective assessments of joint function at the times when the subjects return to clinic for their postoperative visits.

Subject payment: Subjects will be paid $1000 with pro-rated payment steps (listed below) to study completion. An additional incentive will be provided in the form of the Fitbit at the end of the subject's use in the study. The tablet devices will be returned to each study center for re-use.
Pro-rated payment will be made as follows:

- $300 for completion of the preoperative HPRU study visit,
- $50 for completion of questionnaires 2 months after surgery (HPRU or Davie Medical Center)
- $50 for completion of questionnaires 6 months after surgery and return of study supplies (electronic tablet, charge, wireless internet card) completed in the HPRU or Davie Medical Center
- $200 for completing at least 90% of the daily diary entries on the electronic tablet and wearing the accelerometer weeks 1 through 8 at least 90% of required time
- $400 for completion of all the scheduled study visits and postoperative assessment/questionnaires (At the end of the 6 month assessment: the electronic diary must be returned (including the charger) and the wireless card for compensation to be processed)

If a subject withdraws for any reason from the study before completion they will be paid according to the schedule of payment above. The accelerometer and the tablet must be returned if a subject withdraws from the study prior to completion for payment to be processed for the portion of the study completed.

To encourage good effort on the Iowa Gambling Task (IGT), a yearly raffle (after 40 completed subjects) of $500 will be held. All subjects who complete the IGT will have one raffle ticket entered into the drawing, regardless of net earnings. In addition, each $100 of net earnings will earn the participant an additional raffle ticket. For example, if a subject completes the IGT and has net earnings of $300, he/she will have four tickets entered in the raffle. Prior research suggests that providing monetary reinforcement on the IGT improves overall performance and reduces performance variability. (Fernie G, Tunney RJ. Some decks are better than others: The effect of reinforcer type and task instructions on learning in the Iowa Gambling Task. Brain and Cognition. 2006;60:94–102.)

Analytical Plan

Data analysis. The plan of analysis and sample size estimation for the primary analysis is presented in full detail in the Bioinformatics Core (Appendix). Briefly, we will examine the frequently obtained (i.e., daily, then monthly) worst daily pain intensity score and the total daily (i.e., non-sleep) accelerometer movement score. One growth curve model will be created for each outcome (pain, movement) using all of the predictors in Table 2, strength of conditioned pain modulation (CPM) from the laboratory session. Additionally, one model that combines both outcomes will examine for lagged and synchronous relationships between the two outcomes (i.e., do changes in one outcome predate changes in the other?). See the Bioinformatics Core for details about the handling of nuisance variables (e.g., site effects, surgeon), missing data, and sensitivity analyses. 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., C-A state), and pre-stimulus baseline pupil diameter (i.e., LC activity). The association between C-A state and pain reporting will first be examined, and in a later block the moderating effect of baseline pupil size will be entered. Statistically significant interaction between baseline pupil diameter and the relationship between C-A state and pain reporting will be interpreted as support for the primary hypothesis (1). Primary hypothesis (2) will be tested by comparing placebo to gabapentin resting pupil diameter after controlling for condition and stimulus intensity. Secondary analyses will include the effect of drug and C-A state on condition. Please see the Bioinformatics Core for more details as well as for statistical power considerations.

We assume that the mechanisms underlying this association are the same in total knee arthroplasty and total hip arthroplasty patients, but that the two groups will have different intercepts (pain at discharge) and slopes (recovery times after surgery). These surgical differences will be modeled using an additional fixed effect for intercept and slope in our primary model. We do not expect these additional fixed effects to be correlated with the predictors used in the primary hypothesis, so the original statistical power calculation is unchanged. We will modify the statistical analysis plan to reflect these changes in the expected statistical model.

Outcome Measure(s)

Primary outcome measure: Modeled trajectory of recovery from pain using a log of time form.

Several secondary analyses are planned that examine changes in cognition (e.g., impulsivity, attention) as well as kinesiophobia. The cognition measures (Iowa Gambling Task, Wisconsin Card Sort, TSK) collected at baseline, , 2 months and 6 months after discharge will be examined using generalized linear model with Time (BL, , 2mo, 6mo) as a fixed factor. Please see the Bioinformatics Core for complete details. Finally, we will collect and secondarily examine biomarkers for stress and noradrenergic functioning by exploring the relationship between preoperative patient characteristics, including psychophysical responses to pain processing and CSF concentrations of norepinephrine and markers associated with stress.

Human Subjects Protection

Subject Recruitment Methods

Appropriate subjects will be identified and approached in the Department of Orthopedics during their regular scheduled appointment, by research personnel. Research personnel will utilize a private exam room to talk with subjects. Subjects will be given the study details and the opportunity to read the informed consent. The subject may take the informed consent home and make their decision regarding study participation. Contact information for the research staff will be provided to the subject so that they may call for questions or to participate. Study personnel will make every effort to approach any subject that will be scheduled for primary TKA or THA.

Informed Consent

Signed informed consent will be obtained from each subject. Research personnel will obtain informed consent, the subject may sign the informed consent during their appointment time in the Orthopedic Clinic or the informed consent may be reviewed and signed during their first scheduled visit to the Headache and Pain Research Unit (HPRU). If the subject has signed the informed consent prior to their first HPRU visit, consent will be confirmed and all questions answered prior to any study procedures. No study information or procedures will be performed prior to the subject signing the informed consent. All subjects will be given a copy of the signed, informed consent.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Risks.

The thermal heat testing may be discomforting (however, subjects are not exposed to temperatures greater than they would experience in everyday life.) The heat probe can cause a temporary redness of the skin for several hours. The risk of burn is very remote. We will remove the probe any time the subject requests. The subject may also move their extremity away from the thermal heat probe at any time. The device is a computer controlled, water cooled device that has safety mechanisms in place to prevent extreme temperatures from being utilized. Additionally, we have used this device for > 10 years and have not had any reported burns.

Pulmonary

Gabapentin has been associated with serious breathing difficulties in patients taking opioids and those with diseases that reduce lung function including chronic obstructive pulmonary disease (COPD). Symptoms include confusion, unusual dizziness or lightheadedness, extreme sleepiness, slowed, shallow or difficult breathing, unresponsiveness, and bluish colored or tinted skin, especially on the lips, fingers, or toes.

The most common side effects (greater than 2%) of gabapentin are listed in the table below:

Body System/Preferred Term	Neurontin® N=336	Placebo N=227 % %
Body as a Whole		
Asthenia	5.7	4.8
Infection	5.1	3.5
Headache	3.3	3.1
Accidental injury	3.3	1.3
Abdominal pain	2.7	2.6
Digestive System		
Diarrhea	5.7	3.1
Dry mouth	4.8	1.3
Constipation	3.9	1.8
Nausea	3.9	3.1
Vomiting	3.3	1.8
Flatulence	2.1	1.8

Metabolic and Nutritional Disorders		
Peripheral edema	8.3	2.2
Nervous System		
Dizziness	28.0	7.5
Somnolence	21.4	5.3
Ataxia	3.3	0.0
Thinking abnormal	2.7	0.0
Special Senses		
Amblyopia[a]	2.7	0.9

[a] Reported as blurred vision

Other events in more than 1% of patients but equally or more frequent in the placebo group included pain, tremor, neuralgia, back pain, dyspepsia, dyspnea, and flu syndrome.

The incidence of depression and confusion were reported as frequent (defined as occurring in at least 1/100 patients).

Safe chronic ocular exposure values to Infrared, Range A (IR-A), are in the range of 10mW/cm^2 or below. The largest eye irradiance noted with the near infrared recording system that will be utilized for this protocol is between 0.75 - 0.80 mW/cm^2 at the plane of the eye. Under normal use, eye irradiance is between 0.1 – 0.3 mW/cm^2.

Protections Against Risk From Providing Data.

- Data security: Electronic data will be maintained in a password protected database, on password protected servers, to which only the study team has access. Daily hand-held data is de-identified, and is transferred to lab computers via a secure connection. REDCap is a HIPAA compliant, secure database system. Data validity will be maintained by validity criterion in the database, and errorchecking procedures. Study staff will complete training in HIPAA regulations, and will be clearly instructed not to divulge confidential information regarding subjects. The system will also be developed in accordance with FDA Part 11 [21CFR11] guidelines. Participant records are kept confidential, with paper records in a secure location and computer records password protected, available only to study staff.
- CSF will be obtained by a board certified anesthesiologist during the course of routine care in providing spinal anesthesia.
- Symptoms of depression, anxiety, and other forms of psychological distress symptoms are to be measured upon enrollment. Because many patients will endorse some level of distress, and it is impossible to know for each individual when they require or are even open to mental health assistance. Therefore, and because our questions may focus patients attention on these sources of significant distress, we will offer a referral to a mental health professional to ALL patients. To be specific, we will provide all patients with telephone numbers and addresses of at least three local mental health resources. We will not explicitly seek suicidal ideation. Patients spontaneously endorsing thoughts of harming themselves or others will have their treating physician informed for an assessment if they need to be guided to the emergency room, or other care pathway.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

The DSMP outlined below will provide appropriate oversight and monitoring to ensure the safety of participants, the validity of the data, and make intermittent recommendations whether to continue, modify or stop the study. The DSMP will utilize an independent DSMB to ensure the effective institution of the DSMP.

This DSMB will have discretion to unblind any results, or conduct any inquiry needed to ensure the safety and efficacy of the trial at the request of the DSMB chair. The committee will maintain a written record of its meetings.

Scope of Data Monitoring

The primary source of the data will be the entered questionnaire data and adverse event reporting.

Study admission data

Monitoring of admission data will include the number of subjects requesting participation in the study, number of subjects screened and number of subjects admitted to the study. The DSMB may request a report of the reason why subjects were disqualified from participating in the study. For subjects admitted to the study, the DSMB will review eligibility criteria for admitted subject, any protocol deviations and/or violations, and the demographic distribution of the subjects by group.

Protocol Compliance

The DSMB will monitor the data to assess compliance with the protocol including the adherence to the randomization schedule. The DSMB will also monitor the quality and completeness of the data being collected, including the frequency of missing or erroneous data, and presence and frequency of outliers.

Safety Data

Monitoring of safety data will include review of Adverse Events (AEs) and Serious Adverse Events (SAEs), trial retention, and reason for drop out. Safety information will be reported to the DSMB in an unblinded manner. Formal statistical analyses of the safety data may be requested by the DSMB. For SAEs, data will include all the adverse event data meeting the FDA definition of serious adverse events. In the assessment of SAEs, the DSMB will review each individual case including treatment group assignment. After each meeting of the DSMB, the secretary will forward a summary report of all serious and unexpected adverse experiences to the principal investigator to summarize the DSMB's review of the serious and unexpected adverse events reported. Furthermore, the DSMB will make a recommendation to continue, modify or halt the study protocol. This report will be transmitted to the Wake Forest University IRB and NIH. Safety data will be prepared for review following the enrollment of each 40 subjects.

Establishing a DSMB Board membership

The DSMB will be appointed by Dr. Eisenach and Dr. Houle with the purpose of reviewing, approval, and monitoring the implementation of the DSMP. The DSMB will have three members encompassing multidisciplinary expertise who are not involved in the study protocol. Board members will have no financial and/or scientific ties to the outcome of the clinical trial to avoid any real or perceived conflict of interest. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data. The DSMB will include the following physicians; Peter Pan, M.D., Professor of Anesthesiology, Robert Weller, M.D., Professor of Anesthesiology and Dennis Ang, M.D., Associate Professor of Rheumatology and Immunology.

Board meeting schedule
The board will have scheduled meetings twice a year and expedited meetings to review unexpected SAEs or other urgent issues that may arise during the trial. Unscheduled meetings may be initiated by the DSMB chair, Dr. Eisenach, or Dr. Houle. The data to be reviewed by the DSMB will be available to the Board members.

DSMB Recommendations:
DSMB recommendations will be made in writing by The DSMB chair to Dr. Eisenach. The secretary will prepare meeting minutes for inclusion in the DSMB report. The draft report will be reviewed by all Board members prior to issuance of the final report. DSMB recommendations will then be forwarded to the NIGMS program officer and Wake Forest University IRB.

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

Appendix
1. Bioinformatics Core
2. Copies of each questionnaires or surveys that will be used
3. Debriefing statement

References

1. Alnaes, D, et al. Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. J Vis 2014:14;1-20.

2. Althaus, A, Arranz, BO, and Neugebauer, E. Distinguishing between pain intensity and pain resolution: Using acute post-surgical pain trajectories to predict chronic post-surgical pain. Eur J Pain 2014:18;513-521.

3. Brennan, TJ, Vandermeulen, EP, and Gebhart, GF. Characterization of a rat model of incisional pain. Pain 1996:64;493-501.

4. Brewer, BW, et al. Pain and negative mood during rehabilitation after anterior cruciate ligament reconstruction: a daily process analysis. Scand J Med Sci Sports 2007:17;520-529.

5. Chapman, CR, et al. Improving individual measurement of postoperative pain: the pain trajectory. J Pain 2011:12;257-262.

6. Eisenach, JC, et al. Effects of intrathecal ketorolac on human experimental pain. Anesthesiology 2010:112;1216-1224.

7. Eldar, E, Cohen, JD, and Niv, Y. The effects of neural gain on attention and learning. Nat Neurosci 2013:16;1146-1153.

8. Gaudilliere, B, et al. Clinical recovery from surgery correlates with single-cell immune signatures. Sci Transl Med 2014:6;255ra131-

9. Gilzenrat, MS, et al. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cogn Affect Behav Neurosci 2010:10;252-269.

10. Guan, Y, et al. A partial L5 spinal nerve ligation induces a limited prolongation of mechanical allodynia in rats: an efficient model for studying mechanisms of neuropathic pain. Neurosci Lett 2010:471;43-47.

11. Hayashida, KI, et al. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology 2007:106;557-562.

12. Hayashida, KI, et al. Gabapentin Acts within the Locus Coeruleus to Alleviate Neuropathic Pain. Anesthesiology 2008:109;1077-1084.

13. Hood, DD, Eisenach, JC, and Tuttle, R. Phase I safety assessment of intrathecal neostigmine in humans. Anesthesiology 1995:82;331-343.

14. Jepma, M and Nieuwenhuis, S. Pupil diameter predicts changes in the exploration-exploitation trade-off: evidence for the adaptive gain theory. J Cogn Neurosci 2011:23;1587-1596.

15. Kaasa, T, et al. Hyperesthesia one year after breast augmentation surgery increases the odds for persistent pain at four years. A prospective four-year follow-up study. Scandinavian Journal of Pain 2010:1;75-81.

16. Kehlet, H, Jensen, TS, and Woolf, CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006:367;1618-1625.

17. Kim, SH and Chung, JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain 1992:50;355-363.

18. Kurtz, S, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007:89;780-785.

19. Losina, E and Katz, JN. Total knee replacement: pursuit of the paramount result. Rheumatology (Oxford) 2012:51;1735-1736.

20. Marino, EN, et al. Impulsivity but not sensation seeking is associated with opioid analgesic misuse risk in patients with chronic pain. Addict Behav 2013:38;2154-2157.

21. Maxwell, JL, et al. Does clinically important change in function after knee replacement guarantee good absolute function? The multicenter osteoarthritis study. J Rheumatol 2014:41;60-64.

22. Minzenberg, MJ, et al. Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 2008:322;1700-1702.

23. Nahman-Averbuch, H, et al. Waning of "conditioned pain modulation": a novel expression of subtle pronociception in migraine. Headache 2013:53;1104-1115.

24. Peters, CM, et al. Individual Differences in Acute Pain-induced Endogenous Analgesia Predict Time to Resolution of Postoperative Pain in the Rat. Anesthesiology 2015:ePub 01/09/2015;

25. Rakel, BA, et al. Predictors of postoperative movement and resting pain following total knee replacement. Pain 2012:153;2192-2203.

26. Scott, CE, et al. Predicting dissatisfaction following total knee replacement: a prospective study of 1217 patients. J Bone Joint Surg Br 2010:92;1253-1258.

27. Shulman, SA, et al. Measurement of Disability-free Survival after Surgery. Anesthesiology 2015:02/18/2015 ePub ahead of Print;

28. Singh, JA and Lewallen, DG. Patient-level improvements in pain and activities of daily living after total knee arthroplasty. Rheumatology (Oxford) 2014a:53;313-320.

29. Singh, JA and Lewallen, DG. Predictors of pain medication use for arthroplasty pain after revision total knee arthroplasty. Rheumatology (Oxford) 2014b:53;1752-1758.

30. Suto, T, Hayashida, K, and Eisenach, JC. Peripheral nerve injury and gabapentin, but not their combinations impair attentional behavior via direct effects on noradrenergic signaling in the brain. Pain 2014:155;1935-1942.

31. Turk, DC, et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain 2006:125;208-215.

32. Wylde, V, et al. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. Pain 2011:152;566-572.

33. Yarnitsky, D, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008:138;22-28.