ENVIRONMENTAL ENRICHMENT AND PAIN IN RODENT MODELS AND OLDER ADULTS

AN ABSTRACT

SUBMITTED ON THE TWENTY-FIRST DAY OF JULY 2016

TO THE AGING STUDIES PROGRAM

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

OF THE SCHOOL OF MEDICINE

OF TULANE UNIVERSITY

FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

BY

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ABSTRACT

Older adults are prone to experiencing more frequent pain due to surgeries, age-associated diagnoses, and/or accumulated injury. Opioids are the most effective treatment for pain, but negative side effects and age-associated pharmacokinetic and pharmacodynamics changes limit their safe use in older adults. Endomorphins (EMs) are endogenous opioid ligands whose analogs show improved analgesic properties with fewer side effects. This study examines the antinociceptive properties and motor side effects of an EM analog at a high dose in young animals and in isolated (IH) and environmentally enriched (EE) housed older animals. Young mice given high doses of Morphine (MS) and EM analog experienced equal antinociception, but when compared to vehicle animals the MS mice were significantly impaired on a test of motor coordination (rotarod) while the EM animals were not.

In older animals, possible stress-induced analgesia (SIA) was observed in IH animals while not in EE animals. An overall main effect of housing was detected at p≤0.05, and the effect of SIA began as soon as 7 days after housing assignment. Animals in IH or EE given an EM analog were statistically different at p≤0.01, while the difference between IH and EE animals given MS reached only p≤0.05.

In older adults, participants who attended a day program with scheduled activities showed significant decreases from Time 1 to Time 2 in pain intensity and number of medications, and scores were trending toward significance pain control. By Time 2, patients attending the day program had significantly lower scores of pain intensity compared to adults who received in-home services only. Loneliness and isolation decreased in groups receiving either in-home services or attending the day program. In
general, adults who increased services experienced the greatest decreases in pain and psychosocial variables.

This study suggests that the response to EE is similar in both humans and rats and that a careful increase in stimulation is the best practice in activity planning for older adults. Policy requirements for EE in older adults residential and day facilities may positively impact the pain medication consumption in this growing population.
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ACKNOWLEDGEMENTS

To say that it has taken a village to accomplish this is an understatement. I am truly thankful to many people whose help and support has been invaluable during this process: my advisors, Drs. James Zadina and Qingwen Xu, were skilled at helping me take one task at a time and always treated others and me with dignity. Each patiently taught techniques, theory and skill, and pushed me to think in new ways. Drs. Larry Durante and Jill Daniel were available to discuss concepts, pointed me in the right direction, and believed in my goal of earning a PhD and then continuing in a clinical setting. Melita Fasold, Xing Zhang, and Mark Nilges taught and re-taught (and re-taught) many skills and techniques with unending patience. The Aging Studies Program Office was consistently supportive and available. Chantell Harmon Reed coordinated Program for All Inclusive Care for the Elderly (PACE) New Orleans was eager and cooperative in her dedication to improving services for their participants. I am thankful to the Newcomb College Institute and the Emily Schoenbaum grant, which funded a semester of Music Therapy at PACE. Joy Allen at Loyola University New Orleans College of Music and Dr. James Cronin in the Tulane University Cell and Molecular Biology Department coordinated the Tulane University Service Learning component of that project. I could not and would not have survived this process without the support, encouragement, and kindness of my classmates and friends Yan Du, Lauren Jensen, Andrea Jones and Jacob Kendall. I am grateful to be loved by Roy, Jewel, Geoffrey and Diane Roberts, Greg and Felice Sieffert, and Christy Wild. Robin LaVigne is always in my heart. Finally, I am my best self when I’m with my husband and partner, Zac Sieffert. I am so very glad to live this life with you.
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CHAPTER 1: GENERAL INTRODUCTION

PHYSICAL AND EMOTIONAL PAIN

The detailed explanation of pain perception and processing is extremely complex and beyond the scope of this project. However, it is essential to understand that pain has both sensory (touch, mechanical, thermal) and emotional (stress, anxiety) aspects. The processing of nociceptive information has both ascending and descending pathways and takes places in a variety of structures sometimes called the “pain neuromatrix” (Melzack, 1999). This group of structures includes both areas primarily responsible for sensory processing of pain such as the primary somatosensory cortex and also areas primarily responsible for emotional processing such as the amygdala (known for emotion and emotional behavior).

In the ascending pathways, nociceptors on free nerve endings of primary neurons transduce the information, and then start a chain beginning with synapses in the dorsal horn onto projection neurons that carry the signal up the spinal cord and into a series of structures within the brain. These structures perform a wide variety of processes including pain localization and coordination of consciousness in response to pain. In descending pathways, a coordinated network of brain structures influences nociceptive information via downward projections to the spinal cord. In their “Gate Control” theory of pain control, Melzac and Wall (Melzack & Wall, 1965) proposed that the brain emits
signals via the descending pathway that cause circuits in the spinal cord to block or change the perception of incoming afferent stimuli information.

Until recently, the physical perception of pain was treated pharmacologically, while the emotional aspects of pain were most often treated as a separate entity. That is, the translation and transduction between emotional pain and physical symptoms were not broadly understood or considered. Panksepp was the first to use the label, “social pain,” arguing that the social attachment system was the product of more basic systems governing physical pain and thermoregulation (Panksepp, 1998). From this assertion, the link between social attachment and evolutionary survival mechanisms- that to be part of a group ensures survival more so than detachment- was made clear: to express pain is to be rewarded with social assistance (Bowlby, 1973) and, therefore, greater chance of survival (Krebs, Stephens, & Sutherland, 1983). The impact of psychosocial elements upon the physical experience of pain- the somatization- is now understood to be an essential element of the pain experience and one that must be considered and addressed for maximum pain control (Eccleston, 2001; Keefe, Porter, Somers, Shelby, & Wren, 2013; Ochsner & Gross, 2005).

**PAIN AND PAIN CHANGES IN OLDER ADULTS**

The prevalence of any report of pain is between 72.4% (Thomas, Peat, Harris, Wilkie, & Croft, 2004) and 73.5 % (Miro et al., 2007) in community-dwelling older adults and as high as 70% in nursing home residents (Chau, Walker, Pai, & Cho, 2008). Further, the reports of long-term care residents in pain is thought to be up to a staggering 80%, and of those, 25% receive no intervention, pharmaceutical or non-pharmaceutical (Chau et al., 2008). Because pain is most prevalent beginning at middle age and
continues with at least the same rate of prevalence or higher into older ages (Gibson & Lussier, 2012), some degree of discomfort and the burden of its management is an almost inevitable part of aging. The quality of life of older adults is negatively impacted by pain (Katz, 2002) and when not addressed, the number of disturbing consequences includes both psychological (depression, anxiety, cognitive impairment) and physiological (falls, malnutrition) deterioration (Herr, 2011). Pain has additionally been found to affect both cognitive skills and motor function (Lorenz, Beck, & Bromm, 1997) indicating that pain is both a personal and public safety issue.

The number of older adults continues to rise exponentially, with the population of adults 65 years and older in the United States alone expected to reach approximately 71 million by the year 2030 (Prevention, 2003). The study of pain in aging persons and controlling it is has become a global research priority. However, while controlling pain is a worthy goal, the complete absence of pain may also place the subject in a threatening position: because pain may indicate potential tissue damage and to motivate escape behaviors (Gibson & Farrell, 2004), the recognition of pain as a threat is imperative to ensure longevity. Conversely, a hypersensitivity to stimuli would create a hyper-aroused state, sabotaging the natural warning system; management of pain without decreasing necessary survival skills is the goal of effective pain management.

Managing the pain of older adults is increasingly complex with age due to the many varied changes experienced by the human organism as it ages. Gibson & Farrell (2004) reviewed the alterations seen with age in nociceptive pathways, including loss of both myelinated and unmyelinated afferent fibers and an increase in damage to those remaining, possibly leading to a slowing in the early warning signs of pain with which
these fibers are associated. Changes occur in the spinal dorsal horn of otherwise healthy older adults and rats, suggesting these changes are not disease- or damage- but rather, age-associated. In addition to myelination changes, shifts in dendritic arborization patterns and neurofibrillary abnormalities are found throughout the aging brain and brainstem and include those areas typically associated with nociceptive processing (Gibson & Farrell, 2004). Further chemical changes occur with aging: Substance P and calcitonin gene related peptide, both neurotransmitters of afferent nociceptive tracts, show a reduction with age as do levels of dopamine, noradrenaline, gamma-aminobutyric acid, and acetylcholine (Mora, Segovia, & del Arco, 2007). These substances have been linked to either the emotional or physical experiences of pain.

Additionally, psychological changes that occur with age may influence the perception of pain. These may result from intrinsic factors, such as changes to central nervous systems (loss of hippocampal volume, resulting in decreased memory) or extrinsic (changes in housing circumstances which result in increased depressive symptoms). There is considerable evidence of depressive symptoms in older adults, both in institutionalized and community settings (Baugniet, Boon, & Ostbye; Murrell, Himmelfarb, & Wright, 1983). Depression and pain are often co-morbid (Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999) with depressive mood linked to higher pain ratings and lower pain tolerance (Tang et al., 2008) and therefore suggesting a shared common pathways (Blackburn-Munro, 2004). Further, antidepressants are an effective treatment for both conditions (Sindrup, Otto, Finnerup, & Jensen, 2005). In addition to the altered perception of pain, older adults often are different in the way they describe, rate, and report pain. While reports differ, overall, there is an agreement in the
literature that older adults report a reduction in intensity and frequency of pain, particularly in visceral (relating to the internal organs) pain reports (Helme & Gibson, 2001).

Dosing considerations for pain medications in older adults include both pharmacodynamics, what chemicals do to the body, and pharmacokinetics, what the body does to a chemical. In particular, decreased clearance of drug and volume of distribution is particularly associated with aging (Cherny et al., 2001). Pharmacokinetic changes in older adults occur across a variety of organ systems, but the literature on changes in organ function with age has been inconsistent. Changes in the gastric system, blood flow, and chemical absorption rates have been reported (Mangoni & Jackson, 2004); however, results depend upon the population studied, i.e., healthy aged, frail elderly, etc. Additionally, frailty and other, psychosocial variables have been shown to be indicators for altered pharmacokinetics in elderly patients (Klotz, 2009).

**OPIOIDS**

There are three known opioid receptors (OR)- kappa (κ), delta (δ) and mu (μ)- and all are G-protein coupled, seven trans-membrane spanning receptors. Although all have unique effects, agents acting at the μ-receptor have the highest analgesic properties. The μ-OR is the main target for both morphine and the endomorphins and is imperative for inducing analgesia. Mu-ORs are heavily expressed in areas such as the spinal cord, raphe nuclei, periaqueductal grey, amygdala and hippocampus. Several of these areas are part of the “pain matrix” as identified by Legrain et al, 2011. The complexity and diverse functions of these areas indicates that the experience of pain is multi-dimensional, and both physical and psychological.
Opioids, among the strongest known pain relievers, may be exogenous and natural such as those derived from the poppy (e.g., morphine), semi-synthetic as in the case of oxycodone, endogenous and natural such as endorphin and dynorphin, enkephalin and endomorphins, or fully synthetic as in fentanyl, analogs of endomorphin, and other endogenous opioids. Opioids are recognized by the World Health Organization (WHO) as the foundation for treatment of moderate to severe pain (Vargas-Schaffer, 2010). Although three different opioid receptors have been identified, the most relevant to chronic and/or severe pain relief is the μ-receptor, which is the receptor most targeted in opioids used in clinical settings. Opioids bind to their respective receptors found in the brain, gastrointestinal tract and spinal cord, leading to a cascade of intracellular signaling events that inhibit neuronal excitability to reduce pain.

Ancient Greece’s Theophrastus was the first to make written reference to the milk of the poppy plant in the 3rd century BC. Some scholars view the suggestion of its use to ameliorate ailment from 2100 BC to be the first reference as a “prescription.” In the early 1800’s Friedrich Wilhelm Sertürner isolated the single alkaloid compound known as morphine (Schmitz, 1985). Morphine (MS) remains the opioid many clinicians feel is the most conventional choice for chronic and/or severe pain (Cherny et al., 2001) and is so familiar that it is the most frequently used opioid as a reference for all others (Schafer, 2010). In addition to its potency, affordability and ease of administration, morphine’s side effects are also well known. These drugs have the potential to impact several systems including gastrointestinal (nausea/vomiting), autonomic (urinary retention), Central Nervous System (drowsiness, hallucinations, cognitive impairment, and respiratory depression), and cutaneous (itching and sweating; Cherny et al, 2001). In
older adults, motor impairment is especially a cause for concern, as their risk of injury such as fracture increases when patients are utilizing opioids (Vestergaard, Rejnmark, & Mosekilde, 2006). These effects cause physicians to hesitate to prescribe them (Larue, Colleau, Fontaine, & Brasseur, 1995) and cause patients concern when using them. Morphine also increases the response of glia cells, and these cells have been associated with both the foundation and maintenance of pain states (Watkins et al., 2007).

Endomorphins, endogenous peptides found in several areas of the brain, brain stem and spinal cord, show the highest affinity and selectivity for the µ-receptor, the same receptor to which morphine binds (Zadina, Hackler, Ge, & Kastin, 1997; Zadina et al., 2016). Although capable of producing antinociception, agonists for the delta (δ-OR) and kappa (κ-OR) receptors produce side effects such as convulsions and dysphoria that have made these compounds unlikely candidates for clinical use. Our lab has developed synthetic µ-OR agonists based on the endomorphins that provide excellent pain relief, and our research has shown they have significantly fewer side effects in a number of domains than does morphine (Zadina et al., 2016). Reducing side effects may be even further possible when combining the EMs with non-pharmacological interventions such as environmental manipulations.

In addition to pain, depression in older adults is common, with between 51 – 71% experiencing their first depressive episode in late life (Fiske, Wetherell, & Gatz, 2009). Neuroimaging of patients in pain and in those with depression share abnormalities of the limbic and prefrontal cortex (Blackburn-Munro, 2004), making a shared mechanism likely. Non-pharmacological interventions to treat both depression and pain in older adults include daily activities (Chua & de Guzman, 2014; Fiske et al., 2009). This
includes but is not limited to physical activity, meaning a more complex definition of
daily activities such as in that of environmental enrichment may be an accessible option
in the treatment of both depression and pain.

**ENVIRONMENTAL ENRICHMENT**

Conversations regarding environmental enrichment (EE) began as early as 1925
with the discussion of adding apparatus to an animal’s environment (Kulpa-Eddy, Taylor,
& Adams, 2005). Since then, EE has expanded to include a variety of psychological and
housing enrichments, and target outcomes range from biological markers to enhancing
play. The benefits of EE in research animals are wide-ranging and have been applied to
animal models in myriad ways, examining countless physical and psychological
outcomes. The 1985 Animal Welfare Act specifies a number of provisions that must be
granted to animals housed for research such as exercise opportunities and a physical
environment in line with beneficial psychological health. Although originally applied to
non-human primates, most research facilities now include enrichment (Kulpa-Eddy et al.,
2005) for all animals, including nesting material for rodents or complex climbing
structures for primates. In fact, guidelines for EE suggest that when the previous and/or
organic habitat of an animal is known, using it as guidance for developing its captive
habitat it the best course of action (Mellen & Sevenich MacPhee, 2001). Because the EE
in research animals has been the status quo only since the mid-20th century, decisions
regarding how much EE, what type, and for which subjects have been of great debate.
EE for non-human primates is and should not be the same and EE for rodents, zoo
animals not the same as laboratories, etc.
Many investigators have experimented with *types* of EE. That is, many investigators have separated the elements of EE into exercise, objects added to the housing environment, or the addition of a companion. Rosenzweig’s 1978 definition of environmental enrichment (EE) as “a combination of complex inanimate and social stimulation” (Will, Rosenzweig, Bennett, Hebert, & Morimoto, 1977, p. 563) is still widely accepted. In fact, after sorting out the separate elements of EE—socialization opportunities, toys, changing components, and physical exercise opportunities—the research community has come to the conclusion that “no single variable can account for the consequences of enrichment…. Either observing an enrichment environment without being allowed active participation (‘TV rat’) nor social interaction alone can elicit the effects of enriched environments” (van Praag, Kempermann, & Gage, 2000, p. 192). In practice, it seems to be an interaction between these variables—when these things work together—that accounts for the effects of EE as we know it. Here, *lifestyle* is the key concept when considering how EE in animal models may be related to human subjects; the addition of social, exercise and opportunities for new experiences create an overall *lifestyle* modification. In human subjects, this can be enough to change biomedical outcomes, leading researchers to consider this composite *complementary medicine*.

**COMPLEMENTARY AND ALTERNATIVE MEDICINE**

Although both physicians and patients in many countries report using complementary and alternative medicine (CAM) approaches (Joos, Musselmann, & Szecsenyi, 2010) in healthcare, the definition of CAM remains broad. The National Center for Complementary and Alternative Medicine (NCCAM) acknowledges that
defining CAM is difficult because of its broad applications but asserts, “CAM is group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine” (NCCAM, 2013). These may include a variety of activities from hypnosis to prayer (Bruckenthal, 2010). The NCCAM reminds its readers “Complementary medicine refers to use of CAM together with conventional medicine… to help lessen pain” (NCCAM, 2013). Indeed, Bruckenthal’s review (2012) of CAM found that pain was the most common reason older adults utilized CAM, and in addition, the NCCAM found 73% of respondents 50 years of age and older report pain control as the main reason CAM was utilized (Lechtzin et al., 2010).

Pain catastrophizing, negative thoughts and perseverations about helplessness, fear, and similar emotions, has been associated with higher rates of psychosocial distress and pain (Osman et al., 2000). Anxiety and depression are also associated with increased ratings of pain in both acute (Carr, Nicky Thomas, & Wilson-Barnet, 2005; Feeney, 2006) and chronic pain conditions (Tsang et al., 2005). A growing body of literature confirms that addressing anxiety and pain by altering the environment with interventions such as music, prayer, and mindfulness positively influences pain rating (Astin, 2004; Keefe et al., 2013; Morone & Greco, 2007).

In this way, altering one’s environment to maximize the effects of pain medication is CAM, and quantifying the results of this manipulation is of utmost importance to the aging population: less pain medication may translate to fewer dollars spent, decreased management required by caregivers, diminished risk of side effects, and greater quality of life.
Although environment has been shown to alter pain perception in rats, (Aghajani, Vaez Mahdavi, Khalili Najafabadi, & Ghazanfari, 2012; Astin, Shapiro, Eisenberg, & Forys, 2003; Davis, Cortex, & Rubin, 1990; Lechtzin et al., 2010; McGrath, 1994; Schorr, 1993) there remains a paucity of knowledge regarding to what degree environmental considerations should inform the dosage, frequency, or type of pain medication prescribed by physicians. For example, in addition to the standard chart requirements such as diagnosis, age, medications dispensed, etc., states may require residential facilities housing older adults to record the activities in which their residents participate and the frequency but it is not required in all states. This lack of standardization in medical records requirements indicates the minimal consideration participation in activities currently has.

While the exact mechanisms for the wide variety of improvements reported from CAM are not known, Cohen et al (2006) speculate that one main mechanism may be the sense of control and/or self-mastery that participation in the arts provides. In particular, Cohen et al (2006) found that a group of older adults participating in socially engaging cultural activities took less medication than their control group counterparts and experienced fewer falls as well. This is particularly relevant to our study, as growing evidence suggests the sense of control, or self-efficacy, has been implicated in the moderation of pain perception through both opioid and non-opioid systems (Asghari & Nicholas, 2001; Bandura, O’Leary, Taylor, Gauthier, & Gossard, 1987; Morone & Greco, 2007; Wasan, Davar, & Jamison, 2005) and this points to a role for regular engagement in activities in older adulthood.
The role of socialization in pain modulation is also becoming more apparent, with studies showing that the presence of a supportive social network can attenuate pain perception (Cano, Johansen, & Geisser, 2004; Coan, Schaefer, & Davidson, 2006; McGrath, 1994). It is equally important to note the way in which the patient perceives social support: it is beneficial to patient well-being if one perceives social connectedness—a dense network of others with similar demographic characteristics who live in close proximity is associated with positive mental and physical health indicators (Ashida & Heaney, 2008).

Through the combination of social interaction and changing environments, EE engenders a sense of control over outcomes related to the self and the confidence required to self-advocate (Patterson & Perlstein, 2011). One cannot experience this in an isolated, stagnant environment. This sense of control is also known as self-efficacy, and has been inversely correlated with decreased perception of pain and decreased consumption of pain medication (Manning & Wright, 1983). Improved self-efficacy and autonomy leads to greater ability to self-advocate, decreased physiological processes that draw attention to pain sensations (Bandura, Reese, & Adams, 1982), creates a positive loop regarding physical activity (Shoor & Holman, 1984), and leads to overall decreased mortality (Vaaninen et al., 2009). Because endogenous opioids may be activated by psychosocial placebo effects (Levine, Gordon, & Fields, 1978), use of EE in facilities with older adults provides is the perfect opportunity to combine opioid administration with psychosocial interventions, activating both exogenous and endogenous analgesic systems.
The Program for All Inclusive Care for the Elderly (PACE) began in San Francisco’s Chinatown in 1971 in an attempt to provide care for older adults in the Chinese community for whom institutionalized care was not an option. The original model offered, as it does today, both medical and comprehensive psychosocial care, rehabilitation and respite care. The flexibility to meet the needs of a wide variety of elders made the On Lok model (“peaceful happy abode”) successful and this example became the PACE standard. The PACE philosophy today is still that of assisting elders with aging in their own homes, although they meet the standards of requiring nursing care and are likely to need ongoing care for the remainders of their lives.

Several studies have documented the efficacy and cost effectiveness of PACE interventions. Mukamel et al (2007) analyzed relationships between participant health outcomes and individual PACE program characteristics. The variables most associated with higher functional outcomes of participants were staff training, interdisciplinary team coordination, and staff cultural similarity and sensitivity to its participants (Mukamel et al., 2007). Most relevant to this study, PACE’s capitation model, solvent since its inception (Hirth, Baskins, & Dever-Bumba, 2009), has been found to be less expensive than fee-for-service models (D. Wieland, Kinosian, Stallard, & Boland, 2013) and, rather than offering services only to the sickest or healthiest, lower client mortality was associated with providing equal services to all of its members (Mukamel et al., 2007).

Compared with nursing home and an in-home services-only-program, PACE participants were found to be sicker, yet still lived longer. Research suggests this is
attributable to the PACE medical-home model of interdisciplinary-team-managed care (Wieland, Boland, Baskins, & Kinosian, 2010). Additionally, although black PACE participants have a lower functional status upon admission, their survival rate is longer than their white cohorts, with this survival advantage beginning approximately 1 year after PACE admission (Tan, Lui, Eng, Jha, & Covinsky, 2003).

Although it is tempting to provide as many types of services to medically involved populations as often as possible, greater consumption of interdisciplinary care does not always lead to improved health outcomes. Tempkin-Greener et al (2008) found a relationship between more hospital services a center provided and more hospital admissions; however, they also found decreased admissions in centers with more day activities and therapy opportunities (Temkin-Greener, Bajorska, & Mukamel, 2008). These authors suggest that PACE programs with a high number of patients with hospital use should consider the amount and intensity of their day center programming, and propose this may result in even better coordination of care and better health and fiscal results. This implies regular, tailored therapies and activity may confer a protective effect upon sicker patients.

**ANIMAL MODELS**

The study of pain presents measurement and translational considerations. Although human pain rating scales are reliable and accurate, they are subject to interpretation, leading researchers to search for a more objective measurement. However, as of this date, no such measurement has been found; there are over 250 pain-associated genes (Mogil, 2009), and when the variables of environment, diet, and rearing are added, the etiology, development and treatment of pain is limitless. Although differences in a
variety of animal protocols exist including handling, vendor, diet, sex, lighting (Willner, 1984), these variables can all be strictly controlled by the researcher and/or vivarium. Animal behavioral responses to pain, such as licking a paw or flicking a tail away from a noxious stimuli, are therefore interpreted and scored, and have been the dominant paradigm in both basic science experiments and pharmaceutical development (Mogil, 2009).

Animal models have traditionally provided basic research methods to study pain; however, this research is fraught with methodological confounds and complications. That is, results may be influenced by basic considerations such as species, sex, age, etc. and more minute details such as housing and/or lighting conditions, diet, husbandry, measurement techniques, etc. Although most pain studies use adult male rats for their studies, the patient most frequently seen for pain complications is a middle-aged woman (Mogil, 2009). Further, although the observation of behaviors associated with pain such as tail flick, paw licking, etc. is interpreted as a pain response, these behaviors are ultimately interpreted by the experimenter and may therefore be misunderstood. Animal models that most closely represent older human adults would need to demonstrate a pain state that spontaneously develops with age and to which can be added an evoked state to mimic that of an injury. This has, to date, been an impossible goal. Therefore, the search for the most translational models to human pain continues.

The National Institute on Aging (NIH) has made aged animals available to researchers since the 1970’s. Throughout development of aging models, animal strains have become more or less popular, resulting in an excess or dearth of literature using particular strains of research at any particular time. For example, the National Institute on Aging (NIA) originally worked with Charles River Laboratories in 1974 to breed and make available three strains of mice and two strains of rats specifically for aging
research. By 1978, the research community and the NIA recognized that by selecting these few strains for aging research, they had inadvertently influenced aging research toward the diseases these colonies naturally developed, such as cancer, as these were the most available aging models. By this time, use of the Sprague-Dawley rat had all but ceased due to its early health concerns, leaving the F344 rat as the most common strain available, and because of its tendency to develop cancer, neoplasm became the most frequently studied aging-associated illness (Sprott, 1991).

In order to be fully recognized, a model must demonstrate acceptable validity, and this falls into three categories: face, predictive, and construct validity (Tkacs & Thompson, 2006). Face validity- the assurance that the model is representing what is should- has, in the case of EE, been replicated multiple times by a variety of researchers and laboratories in a variety of research and clinical spheres (Belz, Kennell, Czambel, Rubin, & Rhodes, 2003; Del Arco et al., 2006; Moncek, Duncko, Johansson, & Jezova, 2004; Segovia, Arco, & Mora, 2009; Smith et al., 2005; Will et al., 1977). EE has been studied extensively since the 1940’s and has consistently produced results in a variety of both biomedical and psychosocial domains. Further, biomarkers frequently measured in rodents such as corticosterone have analogs in humans (cortisol), lending a great deal of face validity. Face Validity alone doesn’t assure an exact transfer of findings from model to model; however, it does improve this probability.

Predictive Validity- the accuracy of the predicted outcomes in the clinical setting- should also be considered when considering the relevance of a model. In the case of EE, the risk is slight, and in fact, research in both humans and rodents has been ongoing for decades. However, to our knowledge, no literature exists that specifically draws a
comparison between the benefits drawn from EE in rodents and those from EE in humans. Construct validity is perhaps the most challenging, as it seeks to create animal models that will be thoroughly and accurately predictive of human outcomes and, therefore, consider both similarities and differences between the animal and human model, (Tkacs & Thompson, 2006). With proper housing conditions and careful husbandry practices, construct validity can be achieved. Although the animal model differs from humans in many ways, it remains a commonly used model for studying pain (Mogil, Davis, & Derbyshire, 2010). Homogeneity is also a consideration: rats are often inbred and experience the same lifestyle and the same diet. In human beings, each has a unique genetic makeup and therefore a different progression of pathology, both diagnosed and undiagnosed.

One major criticism of animal models is failure and, to some extent, inability, to include human manifestations of pain that include psychosocial measures such as anxiety, depression, etc. Although we may observe some behaviors considered to be indicators of these conditions, not all animals used in pain models display the same acute behaviors, and this is also true in animals experiencing chronic pain (Mogil, 2009). The challenge of pain research, then, is to use animal models to represent human behavior to the best of the scientific ability while keeping in mind the limitation of these models and the inability of them to include rapidly changing variables of human environment and pathology. An added benefit of EE is its practical application (translational) in addition to expansion of the knowledge base (basic science).

**THEORIES OF EE IN HUMANS AND ANIMALS**

Although EE has been commonplace for some time, it continues to suffer from
both methodological and theoretical issues. Methodologically, there remains no standard for EE practices—types of objects, frequency of new objects, number of cagemates, etc., much less species-specific guidelines that have been agreed upon by the research, laboratory and/or veterinarian communities. Theoretically, EE suffers from issues such as agreement upon basic definitions and scientific rigor, such as using hypothesis testing and sound scientific research principles (Lutz & Novak, 2005).

Several disciplines continue to explore to what extent and frequency the environment impacts physical perception and mental health. In social science, the term *built environment* refers to the systems and infrastructure that support human life, e.g., buildings, parks, neighborhoods, etc. More recently, attention has turned toward how the built environment shapes human physical responses such as activity; personal connection, as in social capital; and perception, as in pain. For example, activity may be increased with the additional of infrastructure that supports clear and well-lit walking paths (Sallis, Floyd, Rodríguez, & Saelens, 2012). *Social capital* is the internal and external constructs shared by a social organization that make effective change possible (Putnam, Leonardi, & Nannetti, 1993). In particular, the construct of bonding social capital—the intra-group ties among those who share demographic similarities such as neighborhood, age, race, sex, etc.—may foster connection and social support, leading to improved pain management.

Medical facilities have begun to design treatment and recovery rooms for optimal patient response (Rubin, Owens, & Golden, 1998), and this includes response to pain. In this context, the concept of *built environment* is an appropriate model for understanding human environmental enrichment, as we are referring to the planned addition or lack of purposeful socialization and activity in a day center specifically designed for a particular
Environmental Stress Theory is perhaps the theory that most closely explains the results from environmental enrichment in older adult facilities. In the late 19th century WB Cannon introduced the idea of homeostasis, the concept that the body has a natural point at which it is most comfortable and to which it returns after insult. Environmental stress theory maintains any number of factors in an environment - sound, wind, air quality, etc. - can affect one’s physiological responses and therefore disrupt homeostasis. In information overload theory, the body responds to stress-related hyper- or hypo-stimulation in an inverted U-shaped fashion, releasing a cascade of hormones and psychological defenses to return to its natural state.

Theories of why and how humans and animals respond differently to pain in different environments has been divided and focused within disciplines. In this study, the theories of environmental enrichment, built environment, and environmental stress are synergistic: efforts to provide EE in the built environment (here, appropriate spaces for activities with older adults) affect environmental stress - how much or how little environmental stimulation one processes before it is stressful. While there is a depth of literature on each of these topics, research is scant on if, why, and how animal models of enrichment and pain are an accurate predictor of human response to enrichment and pain, what the next steps may be, and the most responsible ways in which to move forward. EE, and particularly the topic of EE for pain, has a good deal of literature to support its face validity: clinical medical journal contain a good deal of literature on the impact of listening to music, watching videos, having loved ones present, etc. upon pain.

Experimental journals have reported the effect of EE on recovery from injury, and the
mechanisms of EE have been studied via bench science methods. However, construct and predictive validity literature remain lacking.

**TRANSLATIONAL RESEARCH**

Translational research includes two areas of focus. The first is applying knowledge gleaned during laboratory or bench science studies and preclinical research to human trials. The second is adopting research with the goal of creating best practices and policy recommendation for the community, including prevention and cost-effective treatment strategies (Rubio et al., 2010). Moving from preclinical to clinical, “bench to bedside” is the second phase of translational research (Horig, Marincola, & Marincola, 2005). This phase should make scientific innovation experienced in a laboratory setting accessible on a population level (Zerhouni, 2005) and provide solutions to health issues that are practical and sustainable (Lean, Mann, Hoek, Elliot, & Schofield, 2008). To meet its own definition, translational research must blend basic science and clinical research skills and resources, meaning it cannot be fully realized in a single laboratory or clinical setting (Pober, Neuhauser, & Pober, 2001). Rather, translational research is intrinsically multi-disciplinary. Translational research remains the best option the healthcare industry has for delivering modern, informed, modern, collaborative personalized health care (Horig et al., 2005).
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CHAPTER 2: EFFECT OF ACUTE MORPHINE AND ENDOMORPHIN ANALOGS AT HIGH DOSES ON MOTOR AND PAIN IN YOUNG MALE MICE

INTRODUCTION

Pain in Aging

Advancing age often generates both acute and chronic conditions that require pain management. The World Health Organization’s (WHO) pain ladder was originally designed for management of cancer pain, but it is now used for management of pain in general. In the pain ladder, the WHO currently recommends opioids for treatment of chronic to severe pain (Vargas-Schaffer, 2010). While opioids and, in particular, morphine, are well known for their analgesic properties, they are also notorious for the incidence of deleterious side effects including motor impairment and sedation (Benyamin et al., 2008).

The prevalence of pain in older adults residing in facilities is estimated to be between 49-83% (Fox, Raina, & Jadad, 1999) and as high as 74% in community dwelling older adults (Sawyer, Bodner, Ritchie, & Allman, 2006). These numbers indicate a great amount of people in need of pain relief. Furthermore, the prevalence of pain increases with age, and these adults are likely receiving opioid medication.

Aging research by definition searches for changes that occur due in part or in whole to the aging process. When a behavioral or psychological difference is observed in older models without an established baseline in younger models, it is unclear whether the
effect is due to aging or other factors. In fact, the American Federation for Aging Research recommends against using older animals at the start of an experimental series, suggesting instead beginning with younger animals and increasing the age of experimental subjects by cohort if an effect of intervention is found (Miller & Nadon, 2016). This is especially relevant in the study of pharmaceuticals, as aging-associated changes cause both differences in the way the body processes drug (pharmacokinetics) and the way the drug affects the body (pharmacodynamics).

Accordingly, aging-associated pharmacokinetic and pharmacodynamic changes may affect both the analgesic properties and side effects of opioids. Motor impairment as a side effect of pain medication is particularly distressing to the older adult population: falls are the most common cause of both fatal and non-fatal injuries, and cost Americans over $50 billion per year (Prevention, 2012). Further, opioids are associated with fracture risk in older adults (Vestergaard, Rejnmark, & Mosekilde, 2006), suggesting opioids may be involved in a cycle of pain relief that leads to injury, causing more prescription of opioid medication, leading to increased fall risk, etc. Fall-related injuries also account for great deal of morbidity and mortality in older adults (Galizia et al., 2012) and cost the American economy an estimated $30 billion (Control, 2015) per year. Reducing the risk of falling, including by minimizing motor impairment due to medication, is a logical and pressing goal.

**Opioids**

Morphine sulfate (MS) has been used for pain relief for centuries and remains the “gold standard” of relief for debilitating, chronic, and/or severe pain. It continues to remain at the top of the World Health Organization’s analgesic ladder, and in addition to
use in chronic pain relief, is recommend when other medications have failed to adequately control pain (Claxton, Cramer, & Pierce, 2001; Pergolizzi et al., 2008). Morphine’s side effects are also well known and include respiratory depression, cognitive impairment, sedation, and impairment motor coordination, causing many physicians to hesitate in its prescription (Larue, Colleau, Fontaine, & Brasseur, 1995) and patients concern in its use.

Endomorphins (EMs) are endogenous analgesic peptides discovered by Zadina et al in 1997 (Zadina, Hackler, Ge, & Kastin, 1997) that, like MS, also bind to the μ-receptor. Our lab has synthesized stable EM analogs that produce fewer side effects, including decreased motor impairment, relative to morphine and have shown greater analgesic potential (Zadina et al., 2016). This work was done via intravenous delivery (IV) with rats in our lab. In the present study, we chose to use mice for two reasons: 1. Decreased cost: mice are significantly less expensive than rats and, 2. Previous studies have used rats, and efficacy of the compound in more than one animal model increases the likelihood that results will generalize to human models.

The motor side effects of morphine have been extensively studied in a variety of species and found to be biphasic. That is, lower doses of morphine stimulate locomotion while higher doses attenuate it (Patti et al., 2005). Morphine’s impact on older adults is of great concern, particularly if it causes stimulation of locomotion or decreased motor ability as indicated in the rodent models. Fall risk associated with hospitalization is responsible for a significant amount of morbidity and mortality (Chisholm & Harruff, 2010). Aging mammals experience physiological changes in pain pathways with age that alters both the perception of pain and the medication required alleviate it (Gibson &
Farrell, 2004). Morphine’s dosage should begin “low and slow” (Kahan, Mailis-Gagnon, Wilson, & Srivastava, 2011), aiming for the lowest dose that controls pain in order to incur the fewest side effects. However, patients at end of life, those with chronic and/or intractable pain, and those with severe pain often require amounts of opiates higher than typical doses (Bercovitch & Adunsky, 2004, 2006; Mishra, Bhatnagar, & Singhal, 2007), indicating a clear need for opioids that may be safely given at elevated doses. As the dose increases, so too does the incidence and severity of side effects (Jacobson, Chabal, & Brody, 1988), making the spectrum of therapeutic doses extremely broad. To our knowledge, no studies exist examining the impact of high doses of morphine and the EMs upon motor performance in mice. In order to fill this research gap we elected to test high doses of morphine for both antinociception and impact upon motor skills.

**Motor Testing**

Many studies of both acute and chronic pain have characterized the impact of opioids on motor performance in rodents via the rotarod test. These studies typically employ a training period of 2-3 days followed by a testing period. The training & testing usually consists of gradually increasing rotarod rotations per minute (RPMs) up to a predetermined cutoff point of between 60 seconds and 3 minutes (Cartmell, Gelgor, & Mitchell, 1991; Meert & Vermeirsch 2005). The rotarod has been used as a method for measuring coordination and motor learning for approximately 40 years (Watzman, 1964; Pritchett, 2003) and is widely recognized as a standard measurement in the literature. While this method is effective at demonstrating motor impairment within a set time frame, it does not account for any additional learning or stamina improvements that may occur with consecutive training days. In other words, animals that may have continued to
improve with additional training days or a longer period before cutoffs are unable to display such motor learning or stamina because the cut point prevents them from demonstrating it.

Animals are usually trained to species- and age-specific criteria that represent proficiency, followed by the administration of a drug, injury, or behavioral condition, and then re-tested on the rotarod. Responses to changes in rotarod speed or duration indicate the impact of the intervention upon motor performance. Importantly, the rotarod has been found sensitive enough to consistently detect impairment that other assays do not (Hamm, Pike, O'Dell, Lyeth, & Jenkins, 1994) and therefore remains one of the most commonly used test of locomotion ability and impairment. When young animals are used, fatigue is less of a concern that with aged animals, and using an accelerating rotarod protocol in which the speed and duration slowly increases protects against learned apathy (Brooks & Dunnett, 2009).

The majority of literature on rotarod tests employs a cutoff time of 180 seconds; however, the training of animals to become proficient on the rotarod has been a source of some concern regarding innate ability and the variation between animals. That is, animals are trained to walk or run on the rod until a pre-determined speed and/or time has been reached; however, within any species there are intrinsically good and poor performers. It is possible, then, that a pre-determined cutoff time would not have represented the typical variance in the sample. Further, ending a test before animals are truly fatigued may disguise whether results indicate the true nature of the drug’s side effects or reflect the animal’s actual motor ability. In order to capture the broad range of abilities, we expanded running time to 500 seconds. This allowed a fuller picture of the
impact of drug upon motor from onset to abatement of analgesia and captures a broader range of motor capabilities of a set of animals.

**Antinociception and the Tail Flick Test**

The Tail Flick (TF) paradigm tests antinociception via the spinal tail flick response (described in *Materials and Methods*, below). The TF has been used in a number of protocols for many years, and the pharmacology community in particular has reached a consensus in determining its efficacy and efficiency for measuring the impact of opioids. (Bars, Gozariu, & Cadden, 2001). We therefore elected to continue its use in determining the analgesic properties of the EMs.

Previous work in our lab has compared motor side effects of morphine to equi-antinociceptive doses of EMs in rats and reported fewer motor side effects with the analogs (Zadina et al., 2016). Morphine-induced motor impairment in mice is observed at much higher doses in mice than in rats. This study sought to clarify the impact of MS vs. EM analog upon motor coordination in mice. We hypothesized some motor side effects would occur but that impairment would be less than that observed after equi-analgesic doses of morphine. Further, using a subcutaneous (SubQ) route of delivery, rather than an intravenous or intracerebroventricular, allowed for less invasive administration and further characterization of clinically useful routes of administration.

**MATERIALS AND METHODS**

**Animals**

Young, male CD1 mice weighing 18-21 grams were obtained from Charles River Laboratories (Wilmington, Massachusetts) and acclimated to our vivarium for 2-5 days after arrival. During this period, the researcher handled mice for 5-10 minutes per day to
minimize any stress confounders that may occur due to handling during later testing. The vivarium utilizes a 12-hr light/dark cycle (8 a.m.-8 p.m.) and food and water were provided ad libitum. Per vivarium standards, animals were housed in a plastic transparent cages with dimensions either 14 ⅜” x 5 ¾” x 4½” or 11” x 7” x 4½” and with shavings and a cotton pad for shredding. Cages were changed once per week. No additional artificial environmental enrichment materials were included in cages; however, all animals were group housed (5 mice per cage).

**Devices**

Motor coordination was tested using Columbus Instruments (Columbus, OH) Rotamex-5 rotarod (Figure 1). The rotarod was programmed to begin at 12 rotations per minute (RPMs) and increase gradually 1 RPMs each 5 seconds, with a maximum speed of 50 RPMs.

![Columbus Instruments Rotamex-5 Rotarod](image1.jpg)

*Figure 1. Columbus Instruments Rotamex-5 Rotarod. Latency to fall and speed are automatically recorded as an indication of motor coordination.*

The machine used for antinociception assessment was the Life Science (Woodland Hills, CA) Series 8, Model 33T tail flick apparatus (Figure 2). This machine emits a hot
beam of light directly onto the tail of the animal. Upon sensing the heat, the animal experiences a reflexive flick of the tail away from the heat source, the heat automatically stops and the time is recorded. The duration of light was set at 9 seconds to prevent unnecessary tissue damage, and intensity was set at 60 to produce a 4-6 second tail flick.

Figure 2. Life Science Tail Flick. Latency to flick tail following exposure to a beam of light is automatically recorded as an indication of antinociception.
Training

Immediately prior to training, animals were acclimated to the testing room each day for approximately 30 minutes to ensure all animals were awake and alert. During training, animals were placed upon the tail flick apparatus (without heat) for approximately one minute to minimize stress and then were taken directly to the rotarod portion. Rotarod training took place over two days and consisted of two sessions per day (one in the morning and one in the afternoon) with 10 training trials per session. The rotarod was programmed to begin at 12 rotations per minute (RPMs) and increase gradually 1 RPMs each 5 seconds, with a maximum speed of 50 RPMs. All animals stayed on as long as possible or until 500 seconds had been reached, whichever came first. Both speed and duration were recorded after each animal fell from the rotarod or when the trial was completed. If an animal completed three successive trials, it was removed and returned to its home cage; a rest period of at least 30 seconds was given between each trial. All subsequent sessions for animals who trained to criteria (3 successive trials completed) were limited to two practice trials in order to ensure maintenance of skill without overtraining. The majority of animals improved during training, with approximately 80% training to criteria.

Chemicals

The National Institute of Drug Abuse (NIDA) provided MS. EM analog was synthesized by the American Peptide Company (Sunnyvale, CA). Both drugs were dissolved in 20% polyethylene glycol/saline and injected at 3 mg/ml.
**Dosage & Testing**

All animals received a subcutaneous bolus dose of MS, EM, or saline at 32 mg/kg. Drugs were injected into the fold of skin gathered from the dorsal superior surface. TF and rotarod testing took place every 15 minutes following administration.

**Analysis**

All data were analyzed with GraphPad Prism Software using an Analysis of Variance (ANOVA) with post-hoc Bonferroni corrections.

**RESULTS**

![Graph showing latency to TF over time for MS @ 32 mg/kg, EM Analog @ 32 mg/kg, and vehicle @ 32 mg/kg.](image)

*Figure 3. Tail flick scores of MS, EM Analog, and vehicle @32 mg/kg. Doses were equi-antinociceptive throughout testing.*

**Analgesia**

Animals who received 32 mg/kg of the EM analog displayed equi-antinociceptive responses to animals who were injected with 32 mg/kg MS (Figure 3). This remained throughout the duration of testing. A group (drug) x trial ANOVA showed a significant effect of drug (p<0.05). Post hoc tests showed that both MS and the EM Analog
treatment produced significantly higher scores than vehicle for 155 minutes, p≤0.05. At 155 minutes, differences were no longer significant.

**Motor Performance**
Rotarod performance generally improved (longer latency to fall from rotarod) for all groups over the course of post-drug testing. However, MS significantly impaired motor behavior (shorter latency to fall) relative to vehicle.

![Graph showing latency to fall from rotarod](image)

*Figure 4. MS, but not EM Analog 4, impairs motor coordination as determined by latency to fall from the rotarod.*

The difference between MS and vehicle, but not vehicle and EM analog, was significant at p ≤ 0.001 @ 80 minutes (Figure 4). A significant difference in motor performance (p < 0.05) was detected between the saline and MS groups, while no difference was detected between the EM and saline animals.
DISCUSSION

Cohort Differences

During the course of this experiment three groups of mice were used. Coinciding with this experiment the vivarium reopened after an extensive renovation, resulting in the second group of mice being housed in this new space and with a different type of cage than the first group. The new cage was several inches larger than the first and the mice did not have to be touched by human hands to have access to water. This is a significant change in environment between cohorts. Later mice displayed behavior statistically and observationally different than other groups of mice in all previous experiments, i.e. those mice housed in the “old” vivarium. Possible reasons for these changes could be the different cage size, exceptionally high personnel traffic, a largely empty animal room, less interaction with staff due to ease of changing equipment, or lighting and sound issues in the renovated space that had not yet been resolved. For these reasons, data from this group of mice were excluded and only mice from the “old” vivarium were included in the analysis.

Translational application

Most of the previous work in our lab has focused on intravenous or intracerebroventricular delivery of drug; however, SubQ delivery offers excellent translational capacity. Unfortunately, the road to a novel drug’s availability is between 10-15 years (Arneric, Laird, Chappell, & Kennedy, 2014); creating a new formulation in tablet or pill form will take additional time, money and research and development resources. The SubQ formula used in this study is equally as effective but safer than MS, making the application of this study relevant and timely.

Additionally, patients themselves can execute a SubQ injection. The delivery of
medication via self-injection for painful conditions such as rheumatoid arthritis (Keininger & Coteur, 2011), migraine (Weidmann et al., 2003), multiple sclerosis (Cramer, Cuffel, Divan, Al-Sabbagh, & Glassman, 2006), HIV (Green et al., 2002) and other conditions has become more desired and commonplace. As life expectancy continues to grow and older adults have more chronic conditions to manage, we may expect to see more demand for a patient-controlled, SubQ pain medication for chronic and/or severe pain. Additionally, in more acute and crisis situations, SubQ delivery offers immediate and long-lasting analgesia with fewer motor side effects, posing an excellent opportunity for use in emergency situations.

Last, self-efficacy, first defined by Bandura (1977), has been shown to be a powerful mediator of pain perception. Self-efficacy refers to an individual’s assessment of his/her ability to behave in ways that will engender desired rewards. Indeed, Bandura applied his original 1977 theory of self-efficacy to pain control: patients who had been taught cognitive techniques to control pain (and therefore acquiring increased self-efficacy) displayed evidence for both endogenous opioid and non-opioid mechanisms. The difference was attributed to the change in perception of control between trained (high self-efficacy) and untrained (low self-efficacy) groups. With detailed patient education and careful dispensation of drug, the SubQ EM formula effective in this study may be straightforwardly accessible to patients for their own self-injection, increasing patient control and therefore self-efficacy over their own symptoms and treatment.

The National Institute of Health (NIH) has made translational medicine a priority (Health & Health, 2015), yet few researchers and clinicians fully agree upon its meaning. Translational medicine has traditionally meant “bench to bedside” and referred to
medications progressing from research laboratories to patients’ medicine cabinets. As the medical and research communities continue to evolve, however, we have come to understand that translational medicine includes both biological and psychological considerations of drug actions, with self-efficacy among them.

**Variability**

Subject variability is an inherent complication that arises in both animal and human studies. Modifying the traditional rotarod paradigm to allow subjects to run for 500 seconds rather than a more standard 180 seconds allowed for the inclusion of superior, average, and inferior performers. This is an important consideration for several reasons.

First, there are both skilled and poor performers in the human population. The effects shown in a variable population of rodents can be assumed to predictive for a similar population similar- in this case, the human population, which is also highly variable. Analgesic medications are among the most commonly prescribed and utilized medications available, and people of all ages and abilities will presumably use the EMs. Secondly, the field of aging is frequently complicated by high variability in its subjects (Mangoni & Jackson, 2004); without a highly variable model (here, mice), translation to another highly variable population (older adults) would not be ethical or logical. Last, older adults at end of life are frequently given high doses of morphine (Sykes & Thorns, 2003); the EMs, then, as alternatives to morphine, may be given in high doses as well.

**CONCLUSIONS**

In this study we have shown that a high SubQ dose of an EM analog showed similar antinociceptive efficacy but had fewer motor side effects than morphine. This
suggests that EM analog may be a safe and effective medication for older adults.

Because this study was conducted with young, male rodents and differential results were found, this suggests further research with female, aged, and aged female rodent models is warranted.
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CHAPTER 3: EFFECTS OF ENVIRONMENTAL ENRICHMENT AND OPIOIDS ON PAIN, MOTOR, ANXIETY AND SPATIAL MEMORY IN OLDER ANIMALS

INTRODUCTION

Pain Sensitivity in Older Animals

Like humans, rodents experience cognitive and physical changes with age (Bizon et al., 2009; Frutos, Pistell, Ingram, & Berthoud, 2012; Janicke, Schulze, & Coper, 1983; Phillips, 2010; Shukitt-Hale, Mouzakis, & Joseph, 1998). Although age differences in response to pain may be influenced by the pain test used (Jourdan et al., 2000), several experiments report an age-associated response to pain, suggesting older rats are more sensitive to pain than their younger cohorts and experience sensitivity dependent upon the type of pain (neuropathic, thermal, etc.) (Chan & Lai, 1982; Crisp et al., 1994; Gagliese, 2009; Gagliese & Melzack, 1999; Jourdan et al., 2000; Kramer & Bodnar, 1986; Yezierski, King, Morgan, Carter, & Vierck, 2010). The response of older animals to μ-receptor analgesic medications has also been studied, with reports of older animals requiring more medication to produce analgesia (Crisp et al., 1994; Jourdan et al., 2000; Jourdan et al., 2002) or reacting in a biphasic pattern (Kramer & Bodnar, 1986). In general, aged animals display different latencies to pain and require more medication to reduce it.
Environmental Enrichment in Old Rats

Rosenzweig’s 1978 definition of environmental enrichment (EE) as “a combination of complex inanimate and social stimulation” (Will, Rosenzweig, Bennett, Hebert, & Morimoto, 1977, p. 563) is still widely accepted. Because of this combination, much research has been dedicated to determining each element’s impact and whether each is independent or additive in nature. Both exercise alone and EE have been found to increase cell survival in the hippocampus and exercise has been shown to be a protective factor prior to neuronal injury (Gobbo & O’Mara, 2005).

In fact, after separating the elements of EE- socialization opportunities, toys, changing components, and physical exercise opportunities- the research community generally accepts the conclusion that “no single variable can account for the consequences of enrichment…[N]either observing an enrichment environment without being allowed active participation (‘TV rat’) nor social interaction alone can elicit the effects of enriched environments” (van Praag, Kempermann, & Gage, 2000, p. 192). In practice, it is be an interaction between these variables - when the elements work together - that accounts for the effects of EE as we know it (Patterson & Perlstein, 2011). For the purposes of this experiment, it is important to note that both inanimate objects placed in cages and additional cagemates increase exercise (Xie et al., 2013). The combination of additional animals and additional objects boosts activity and, therefore, represents the combination Rosenzweig may have had in mind.

EE continues to be an area of study with tremendous popularity and provides excellent translational application as well. For example, because older humans do not usually live in socially or mechanically impoverished, stagnant environments, supplying
animals with EE creates an animal model most closely resembling the human patient. Further, prior rodent studies have found a variety of positive ways in which EE impacts perception on a number of indices, indicating the need for further translational examination of the impacts EE may supply in humans. These results include differences between EE animals and those in isolated housing (IH) in response to pain via thermal (Tall, 2009) and mechanical (Gabriel, Paoletti, et al., 2010) stimulation, with EE providing expedited recovery of functional gross and fine motor behaviors (Gabriel, Marcus, Honig, Helgers, & Joosten, 2009; Lankhorst et al., 2001) and decreased post-operative pain (Gabriel, Marcus, Honig, & Joosten, 2010).

In addition to functional recovery, EE’s impact upon pain has been studied as well. This is essential considering the frequent co-occurrence of injury and pain, the well-documented rise in pain symptoms with advancing age, and a decline in the number of μ-receptors with age (Morley, Flood, & Silver, 1990; Piva, Maggi, Limonta, Dondi, & Martini, 1987). EE is postulated to increase the population of opioid receptors (Smith

Figure 5. Antinociception of EM analogs vs. MS. EM Analog 4 produces antinociception for nearly twice the duration of MS. Dashed lines indicate the response of MS. From Zadina et al, 2016.

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Figure 5. Antinociception of EM analogs vs. MS. EM Analog 4 produces antinociception for nearly twice the duration of MS. Dashed lines indicate the response of MS. From Zadina et al, 2016.
Corrow, 2005), making the possibility of better pain relief via non-pharmacological intervention a real possibility. Previous literature has examined the $\mu$-receptor in dissimilar environments and found EE animals to be more sensitive to low-efficacy mu-opioids (Smith & Corrow, 2005); however, to our knowledge, no studies have been conducted that examine the effect of EE on organically occurring (i.e., non-evoked) pain in aged animals and/or EE on healthy aged animals’ incidence of side effects.

Preliminary studies conducted by our lab have indicated the endomorphin analogs (EMs) synthesized by our group are analgesics that provide greater duration of pain relief relative to morphine sulfate (MS, Figure 5). In addition, these analogs have proven to have a fewer side effects relative to morphine including respiratory depression, motor coordination, cognitive impairment, and abuse potential. The motor coordination results are shown in Chapter 2, Figure 2 and provided the basis for testing whether motor differences would also be observed in older rats.

**Depression, Anxiety and Pain Comorbidities**

Depression and pain are often comorbid issues in adults (Murrell, Himmelfarb, & Wright, 1983), and it has also been suggested there may be a common pathway or mechanism rather than one as a result of the other (Sindrup, Otto, Finnerup, & Jensen, 2005). The hypothalamus-pituitary-adrenal (HPA) axis has been implicated as a common mechanism and link between them (Blackburn-Munro & Blackburn-Monroe, 2001). Neuroimaging of patients in pain and also in those with depression show they share abnormalities of the limbic and prefrontal cortex (Blackburn-Munro, 2004), making a shared cortical mechanism plausible. Changes in environment, such as those evoked by cage changes and novel items, may result in a heightened but steady state of HPA.
hormones that is, overall, more conducive to sudden and stress changes.

Cognitive impairment is another of the major concerns regarding opioid use, and stress has been implicated as a negative influence upon memory formation, perhaps also via the HPA axis. Treatment with antidepressants decreases fear responses and increases exploratory behavior (Buitrago, Schulz, Dichgans, & Luft, 2004). In addition, aged rodents who had been chronically treated with antidepressants performed better on the Morris Water Maze (MWM), perhaps due to decreased glucocorticoid levels (Yau et al., 2002).

Previous rodent studies have focused on the impact of neonatal handling or rearing in impoverished or enriched environments upon anxious behavior in a variety of paradigms. One study found a tendency toward enhanced exploration in novel environments and decreased anxiety in rodents reared in enriched environments (Fernandez-Teruel, Escorihuela, Castellano, Gonzalez, & Tobena, 1997) while others have found little or no difference (Van Waas & Soffié, 1996) between enriched and deprived rats in these same indices. However, these studies were conducted with rats reared either in impoverished or enriched environments. There remains a lack of literature using aged rats placed into EE that use a combination of naturally occurring (aged) and evoked (tail flick) pain paradigms.

**Hypotheses**

H1: EM analogs will produce longer and more potent effects than MS in an antinociception test;

H2: Environmental Enrichment will confer benefits regarding pain and side effects from pain medications. Specifically:
H2a: Environmental enrichment will produce fewer motor side effects (better motor coordination, retention of RR training);

H2b: Environmental enrichment will produce decreased anxious behavior in the Open Field test;

H2c: Environmental enrichment will produce differences in memory formation as reflected in the Morris Water Maze test.

**MATERIALS & METHODS**

**Subjects**
Fischer 344/Brown Norway hybrid (F344xBN) male rats, aged 21 months, were procured from the National Institute on Aging. Upon arrival, rats were individually housed and acclimated to the Tulane University vivarium for 5 days. The vivarium operates under a 12:12 light/dark cycle beginning at 07:00, and all experiments were conducted during the light portion. The Tulane Institutional Animal Care and Use Committee (IACUC) approved all surgical and behavioral procedures and researchers followed the guidelines from the National Institute of Health Guide for the Care and Use of Laboratory Animals.

**Catheterization**
Rats were implanted with an intravenous catheter in the left jugular vein in a manner consistent with our lab’s previous experimental procedures (Zadina et al., 2016) with minor modifications. An isoflurane/oxygen combination was used to anesthetize rats during surgery. An area on the dorsal side of the animal was shaved and cleaned for incision and catheter placement. The catheter was subcutaneously placed onto the back, tubing inserted into the jugular vein, and held with suture. Incision sites were sutured
and antibiotic ointment was applied, followed by a subcutaneous injection of 0.5% lidocaine and 0.25% bupivacaine to address pain. Catheters were flushed daily with 0.1 ml of streptokinase (0.067 mg/ml) to reduce any catheter impediment. Rats were allowed 5 days recovery before being assigned to housing conditions.

**Chemicals**

The National Institute for Drug Abuse (NIDA) provided all MS. EM analogs were synthesized by the American Peptide Company (Sunnyvale, CA). Both drugs were dissolved in 20% polyethylene glycol (3 µg/ml).

**Dosage**

Animals received equi-antinociceptive doses of MS and EM analog. Per previous experiments in our lab and in order to compare dose response curves appropriately, animals receiving MS began at 0.56 mg/kg; EM analog animals began at 1.0 mg/kg. All doses increased every 20 minutes in ¼ logarithm (0.56 mg/kg, 1.0 mg/kg, 1.8 mg/kg, 3.2 mg/kg, 5.6 mg/kg, 10 mg/kg, etc.) until tail flick withdrawal latency reached 9 seconds (cut off time) or until 5 sequential doses were reached.
Protocol Overview

Figure 6. Protocol. After IV surgery, rats were housed in EE or IH for 35 days with motor and pain scores taken every 7 days. Pain and motor testing with drug occurred on day 35, then 2 weeks of drug clearance, open field, and water maze.

Methods

The tail flick (TF) paradigm was used to determine antinociception. This assay measures latency to tail withdrawal from a heat source using a TF device (IITC Life Science, Woodland Hills, CA). The animal is placed on the TF machine and a beam of light is directed onto the tail. Time (seconds) to withdrawal is automatically recorded. Baseline scores averaged between 3-4 seconds; the automatic cut-off was set at 9 seconds to minimize possible tissue damage. Two to three scores were taken and the mean score was recorded.

Rotarod

After 5 days of recovery following surgery, rats were trained on the rotarod (RR) apparatus (Columbus Instruments, Columbus, OH). Each animal trained for two sessions of 5 trials with 10 minutes rest between trials for 5 consecutive days. The RR device was
programmed to begin at a very slow speed on Day 1 and then gradually increase in rotations per minute until a maximum of 13 rotations per minute was achieved. Each day or session began at a slightly faster speed until rats began at 10 RPMs and reached a maximum of 13 RPMs. Starting speed escalated from 4 to 6, 8 to 10 RPM on day 1, 2, etc. and in each case reached 13 RPMs. Maximum time for all trials was 120 seconds. On day 5 of RR training, RR and TF scores were recorded and rats were then assigned to either environmentally enriched or isolated housing (Figure 6). At this time, group assignments were balanced according to RR scores, with equal numbers of good and poor performers in each housing group.

Rats were housed in plastic cages [10.5” x 19” (143 square inches)] and food and water were available ad libitum for all animals. Isolated animals were housed one animal per cage and EE animals were pair-housed. EE animals were provided 1 of 4 objects for environmental enrichment: Gummy Bones, Nyla Bones and Certified Wood Gnawing Blocks, sizes large and small, all from Bio-Serve (Flemington, NJ). Objects were changed once per week with the exception of the last week; enrichment objects then remained in cages until test day.

Baseline RR and TF scores were taken on test day (Day 35). Cumulative injections of MS or EM analogs were given every 20 minutes, followed by 100 µl of saline to ensure full infusion of drug, until a maximum of 9 seconds on the TF or 5.6 mg/kg was reached. Testing continued for 135 minutes, when the majority of animals returned to ≤50% Maximum Possible Effect (MPE) or approximately 6 seconds on the TF test.
**Open Field**

At the end of testing, animals were returned to their original housing assignment and remained in these conditions for 14 days to allow for drug clearance. Four days of Open Field (OF) habituation and data collection followed. The open field is a 100 cm x 100 cm box made of black Plexiglas with an open top. Rats were placed in the apparatus for 20 minutes per day for 4 consecutive days while a video camera mounted above the apparatus recorded movement. Any-Maze software (Wood Dale, IL) was used to divide the field into inner and outer quadrants and track movement. Movement into the inner quadrants is associated with decreased anxiety, while thigmotaxic movement toward the outer quadrants and walls is an indicator of increased anxiety (Prut & Belzung, 2003).

**Morris Water Maze**

The last group of rats participated in a pilot project Morris Water Maze (MWM) project. These rats were not selected or excluded from MWM testing for any behavioral characteristic; rather, the entire group (n=9) was the pilot population. Following previous TF, RR, and OF testing, rats were returned to their original housing conditions and allowed to rest and recover for one week. MWM training and testing was conducted according to a protocol developed by our lab (Jernberg, 2014) with minor revisions. Training was supplemented by a series of visual aids attached to curtains around the pool. Animals were trained 4 trials per day for 5 days.

**Data Analysis**

All data were analyzed with GraphPad Prism Software (GraphPad, San Diego, CA). Tests included two-way ANOVA with a Bonferroni correction, or t-test as appropriate. Open Field data were recorded and collected using AnyMaze software and analyzed with both this program and GraphPad Prism.
RESULTS

Environmentally Enriched vs. Isolation Housing: impact upon Antinociception

A main effect of housing was detected by a two-way ANOVA comparing TF scores of animals housed in EE with those in IH, \( p \leq 0.05 \) (Figure 7). Compared to rats in EE, rats housed in IH showed diminished response to pain as indicated by a longer latency to remove the tail from the heat source. Figure 8 (calculated by two-way ANOVA with Bonferroni post-hoc tests) demonstrates that this difference began as soon as 7 days after assignment to differential housing and reached statistical significance on days 14, 21, and 35, \( p < 0.05, p < 0.001 \) & \( p < 0.01 \) respectively. Further, animals in EE
experienced a statistically significant decrease in latency from days 14 to 21 (Figure 8).

Although both groups experienced significant change, neither group was significantly different from its own initial baseline by Day 35, with only the EE group ever attaining statistical significance (decreased latency) at day 21. There was a significant difference in area under the curve between groups during this 35-day period, $p \leq 0.001$, consistent with the main effect of the overall ANOVA and of less sensitivity to the noxious stimulus in the IH group.

**Effects of Morphine vs. EM analogs**

A two-way ANOVA (drugs by trial, collapsed over housing) shows that when examining same-housed animals on test day only, there are differences only in the EE groups between compounds (Figures 9A and 9B). Post-hoc tests revealed that animals
who received the EM analog demonstrated a statistically significant difference based upon housing at 105 minutes, and a main effect of housing between the groups at $p < 0.01$ (Figure 9B).

**Figure 9.** Antinociceptive response by housing group. A) TF response in IH animals. Differences were not significant. B) TF in EE animals. A main effect of drug was detected, $p \leq 0.01$ and at 105 minutes, the groups were statistically different.
Figure 10. Antinociceptive effects of housing (EE vs. IH) by drug. A) TF in EM analog animals. A main effect of housing was found, \( p \leq 0.05 \), and the difference was significant at 75 minutes, \( p \leq 0.01 \). B) TF in MS animals. No differences were detected.

Animals in the IH group did not show a significant difference in drug response any time point. However, the pattern of antinociception was similar to that of the EE groups, although the EM analog scores were slightly higher than those given after MS from 75 minutes until the end of data collection. In contrast, animals given the EM analog began with antinociception scores slightly below those of MS, by 75 minutes after injection the scores of both drugs overlap, and from that time point forward the EM animals remained at a higher TF score than did MS animals. This difference was significant at 105 minutes, indicating a longer duration of antinociception after EM analog.

A two-way ANOVA, housing by trial, collapsed over drug, detected a main housing effect in the EM Analog animals: figure 10 shows that when given the same drug (MS or EM analog) to animals in different housing groups, EE animals given EM analog display TF scores statistically below IH animals given EM analog, \( p \leq 0.01 \).
Animals given MS were not did not show a significant difference due to housing (Figure 10B).

**Open Field**

Figures 11 & 12 demonstrate that rats housed in the EE condition differ significantly from animals housed in IH in how they explored the environment as measured by the Open Field Test. Figure 11 shows that over 4 days of testing, EE rats spent more time in the inner quadrant (figures 11 A & B, p < .001) and travelled a greater distance (p < .05) than IH rats. EE rats spent longer in the IQ over all (10.581 seconds) from onset of the experiment than did IH rats (5.35 seconds) and moved more in this area as well (2.9072 vs. 1.57905 meters, respectively). The pattern of exploratory behavior was similar in both groups: rising from Day 1 to 2 and Days 2 to 3, but declining between Days 3 to 4 as animals acclimated to the environment and memory formed regarding the escape location.

![Figure 11A](image1.png)

**Figure 11A**

![Figure 11B](image2.png)

**Figure 11B**

Figure 11. Time spent in the inner quadrant. A) Time in the inner quadrant by day and B) Time spent in the inner quadrant, collapsed, ***p<0.001.
Rotarod

Previous literature (Spangler et al., 1994) and our own laboratory experiments have indicated that F344 rats are poor models for motor tests for a variety of reasons and this study confirmed that the same is true of F344 X BN hybrids. The majority of subjects were able to successfully run on the rotarod without falling immediately and sustained several days of increasing speed; however, few trained to criteria. Instead, these aged hybrids seemed to quickly learn they did not have to participate and simply fell to the bottom of the instrument or jumped out entirely without penalty.

Our inclusion measures called for reaching criteria 3 consecutive times reaching 120 seconds at 13 RPMs. Although they were able to complete 2 of the 3 required consecutive sessions, in several cases the rats would refuse to run again, instead going
limp and falling to the floor of the device. Although a rest period was employed, rats that
determined they could fall to the floor of the machine never again completed the task to
120 seconds. This pattern was observed over a number of shipments of animals, months,
and during both morning and evening sessions, indicating a learning effect rather than a
vivarium or colony issue. For this reason, very few animals reached criterion and even
fewer demonstrated retained motor skills throughout the 25 day housing condition;
however, we cannot be certain this is an effect of age, or strain resistance to motor
training. Although these training and testing periods provided valuable information for
future procedures, we were unable to reach a sample size suitable for statistical
comparison.

**Morris Water Maze**

A main effect of housing was detected between groups, p< 0.05. That is, EE
animals who participated in MWM were closer to the location of the submerged platform
during all acquisition training trials than the IH animals (Figure 13).

![Figure 13](image.png)

**Figure 13.** Acquisition of platform learning. In both housing groups, distance from platform decreased
over training. EE animals were significantly closer to the platform than IH animals, p\leq0.05
DISCUSSION

Animals housed in IH environments showed increased antinociception in basal and post-opioid responses as measured by the TF test. Rather than eliciting protective effects of EE, the difference in pain scores between groups of animals may be instead indicative of stress induced analgesia (SIA) in the isolated animals. Isolated housing has been previously shown to increase TF latency (Puglisi-Allegra & Oliverio, 1983) and can be altered by acclimation to a stressful event such as handling. By creating a pain-free state (and one therefore able to flee) SIA has been suggested to be the result of an evolutionary mechanism designed to avoid physical harm and facilitate survival (Kavaliers; Wiedenmayer & Barr, 2000). This phenomenon has been elicited in groups of animals in both chronic and acute pain animal models and in a number of behavioral paradigms (Alleva, Caprioli, & Laviola, 1986; Cornélio, Mendes-Gomes, Fugimoto, Morgan, & Nunes-de-Souza, 2011; King, Devine, Vierck, Rodgers, & Yezierski, 2003; Puglisi-Allegra & Oliverio, 1983). The EE animals in our experiment were exposed to novel objects once per week and were constantly adapting to the behaviors of their cage mates; the IH animals experienced activity once per week when their cages were changed. Because this was regularly scheduled, the same vivarium technician likely completed this task each week. Short exposure to a new environment has been shown to create SIA (Netto, Siegfried, & Izquierdo, 1987). The weekly TF and motor testing may have been infrequent enough to represent an unfamiliar experience and therefore produce an analgesic TF reaction. In animals not practiced in adaptation, this may have produced a marked stress response. Additionally, this infrequency may have caused each weekly
TF/RR measurement to act as a physiological cue to the imminent distress of weekly TF testing rather than a reminder of previous experience and cause for acclimation, further reinforcing the stress response (Fairhurst et al., 2011). Bandura, Cioffi, Taylor & Brouillard (1987) suggested that it is more the uncontrollability and stress factors than the physical pain itself which induces opioid activation.

Several neurotransmitters and neuropeptides have been implicated in SIA, including glutamate, gamma-aminobutyric acid (GABA), cannabinoids, and endogenous opioids (Butler & Finn, 2009; Hohmann et al., 2005). Stress-induced endogenous opioid peptide release has been reported in all of the major opioid systems, and this release causes stress-induced analgesia via action at all receptor types (σ,δ & μ; Al-Hasani & Bruchas, 2011). The combination of endogenous opioids combined with synthetic exogenous opioids delivered by IV may have created the additive response to pain medication seen in IH rats. In other words, animals housed in IH may have had endogenous opioids already “on board.” The exogenous addition of EM analog or MS then more fully occupied μ-receptors. In agreement with previous work (Puglisi-Allegra & Oliverio, 1983) we suspect the IH group then had opioid receptors occupied while the EE group, who had adapted to change, did not experience a significant release of endogenous opioids due to SIA and therefore had only the exogenously delivered EM analog or MS to address pain.

Additionally, EE has been suggested to promoted equilibrium of hormones as through the hypothalamic-pituitary-adrenal (HPA) axis, creating a more predictable and stable chemical response both before and after stress (Belz, Kennell, Czambel, Rubin, & Rhodes, 2003). EE has been shown to alter endocrine function and result in higher basal
levels of corticosterone and adrenaline and in lower levels of these hormones during a stressful event when compared to IH animals (Moncek, Duncko, Johansson, & Jezova, 2004). This may have been the case in our tests, with IH resulting in a higher HPA-axis-triggered-analgesia on test day in the singly housed animals. EE animals may have had higher basal levels of corticosterone and adrenaline but these hormones did not change as dramatically upon challenge, resulting in lower SIA scores throughout many different test conditions—tail flick (pain), rotarod (motor), open field (novelty), and water maze (stress).

Both open field and MWM results indicate EE may confer a benefit during the first phases of training in a new paradigm; however, this benefit is present only during the initial phases and did not carry over into the memory retention phase. That is, EE animals in both the open field and MWM tests performed differently than IH rats; however, the differences disappeared after several repetitions of the task.

A great deal of variation exists in the scientific literature regarding EE and standardization remains a challenge. No specific guidelines exist regarding number of animals per cage, type, or size of novel objects included in cages, frequency at which they should be changed, exercise type, frequency or opportunity, etc. (Fares et al., 2013; Simpson & Kelly, 2011). Changing objects too often may cause a stress-response due to constant novelty; changing them too seldom may also elicit a stress response if well-known objects are replaced. We were unable to locate literature attempting to discriminate between SIA and EE; the line between the two is likely to be different depending upon species, strain, and perhaps sex and age.
Additionally, housing-related, stress-induced analgesia and increased antinociception to morphine in IH animals was found to peak at 30 days (Coudereau, Monier, Bourre, & Frances, 1997; Panksepp, 1980). Our testing took place on day 35 of differential housing and may therefore reflect this crest of maximum differences in pain perception in the IH animals. This maximum effect, however, may be transient.

**Motor Learning**

Our work confirmed that the aged hybrid strain is a poor performer on the rotarod. Aged F344 X BN hybrid animals were fast learners, with a majority from each group easily able to understand and adapt to the steadily increasing RR device during the course of the first training day. However, this learning curve worked against the success of this paradigm, as these animals often learned how to jump out of the rotarod device despite their advanced age and average weight of 500 grams. In F344 X BN hybrids, the rotarod assay must be difficult enough to keep the rats challenged while easy enough to allow for mastery; this extremely small window was impossible to calculate during piloting and the rotarod was therefore unsuccessful with this rodent strain. More testing is needed to characterize the effects of opioids on rotarod in aging rats.

**Spatial Memory**

Our MWM outcomes confirmed other studies regarding learning in this strain (Van Der Staay & Blokland, 1996) showing that aged EE rodents performed better throughout acquisition than did the IH rats. The MWM task is markedly different than the RR task in motivation: rats have no choice but to swim if they do not swim- the apathy displayed in the rotarod is not an option in this protocol. This faster adaptation
may be of great benefit when rodents are placed in a novel location or environment and escape is the only means to survival.

**Strain and Paradigm Effects**

Aging itself frequently elicits an innate pain state (Arneric, Laird, Chappell, & Kennedy, 2014) and is therefore worthy of a model that addresses it. Our study uses the F344xBN strain from the NIA, one of the most commonly used rodent strain in aging studies. Additionally, aging is inherently associated with increased discomfort, increased risk for acute pain, and necessary in- or out-patient procedures to address aging-associated conditions. Our pain model has thus included any inherent pain state associated with aging such as inflammation (Erickson et al., 2010), an acute pain state via the TF assay, delivery of an opioid via intravenous delivery, and psychosocial EE considerations important in the study of pain.

**EE and Translational Research**

Relative to IH animals, animals housed in EE conditions displayed less SIA, less anxious behavior in the open field paradigm, and faster acquisition of the MWM. Although EE has only recently become commonplace in vivariums and animal care practices, this is an important consideration in translational research. Environmental enrichment in humans is standard practice in many nursing/assisted living/independent living homes; however, activities are frequently considered quality of life enhancements rather than a contributor to or mediator of pain control. Before approaching clinical trials, potential analgesics must pass through the discovery and pre-clinical phases. Specifying the conditions under which animals were housed and tested further clarifies anticipated human reaction to analgesics such as the EM analogs. Previous work has
demonstrated that stress hormones that were elevated due to IH may be lowered by EE; this knowledge may inform human pain medication dosage recommendations (Belz et al., 2003).

Advancing age typically necessitates a shift in housing, which in turn affects stress hormones and activity and, therefore, pain perception and medication. This is significant considering the large numbers of older adults who move from individual homes to assisted living or nursing care homes. This transition is stressful at best and traumatic at worst, and adults making this transition display elevated stress hormones for a short period of time (Washburn, 2005). This is likely what the IH animals experienced during cage changes and test day, resulting in SIA. As SIA has been induced in humans as well as rodents (Willer, Dehen, & Cambier, 1981), the translational benefits of EE in older adults can be reasonably extrapolated. When transitioning from one home to another individuals may wish to isolate, it may be to their benefit to balance time alone to process this change (Brandburg, 2007) with engagement with others and participation in a broad variety of activities immediately as they learn a new environment, procedures, routes, room locations, etc.

Further, the difference in dosage is an important one to recognize: polypharmacy (concurrent use of ≥9 medications) increases the incidence of adverse events, including increased healthcare costs, adverse drug interactions and events, cognitive impairment, and falls (Maher, Hanlon, & Hajjar, 2014) and is, unsurprisingly, associated with morbidity and mortality (Hajjar, Cafiero, & Hanlon, 2007). The path to a drug’s availability in the general population can take as long as 15 years (Arneric et al., 2014), leaving a lengthy gap in management of pain during this development. This, and
concerns regarding side effects, indicate the need for non-pharmacological interventions such as EE that would complement and enhance pain medications without endangering the safety of patients.

**CONCLUSIONS**

This study sought to clarify the impact of either in EE or IH conditions on response to pain, drug requirements for antinociception, anxiety, and motor coordination in aged rats. Stress-induced analgesia was higher in all IH animals than in EE animals, and this was stronger in the EM Analog TF response than in MS. Differences in TF scores between IH and EE animals given EM Analog 4 reached statistical significance at \( p \leq 0.001 \), while the difference between IH and EE animals given MS reached only \( p \leq 0.05 \). Additionally, there was no statistically significance between IH and EE animals given MS or EM Analog 4, but there TF scores were higher in EE animals given EM Analog 4 than in EE animals given MS, and this difference was statistically significant at \( p \leq 0.05 \) at 105 minutes after testing began.

EE rats spent less time in the outer quadrant of the open field than did IH rats, and in the Morris Water Maze, were closer to a platform and spent more time in a new location than the IH rats.

These results suggest differential housing changes behavior and response to analgesic medications. Continued research is warranted.


Washburn, A. (2005). Relocation puts elderly nursing home residents at risk of stress, although stress is short lived. Evidence Based Mental Health, 2(49). doi:10.1136/ebmh.8.2.49


CHAPTER 4: THE EFFECTS OF ENVIRONMENT UPON PAIN IN HUMAN SUBJECTS

PAIN IN OLDER ADULTS

Introduction

Older adults are at an increased risk for pain, either due to a history of chronic conditions to manage or because disease and number of surgical procedures increase with age. The prevalence of pain among older adults ranges from 72.4% (Thomas, Peat, Harris, Wilkie, & Croft, 2004) to 73.5% (Miro et al., 2007). Reports of pain in older adults have been shown to increase up until the seventh decade of life (Helme & Gibson, 2001) (Arneric, Laird, Chappell, & Kennedy, 2014) and the number of prescriptions rises with increasing age (Gu, Dillon, & Burt, 2010), yet pain in the elderly remains a poorly understood topic. Aged responses to pain include indications of a decreased tolerance of pain (the maximum level of pain one can tolerate)(Lautenbacher, 2012), yet a simultaneous increase in pain threshold (the point at which the subject recognizes the stimulus as painful). This shift is due in some part to changes in primary sensory neurons (see Chapter 1), shifts in ability to detect damaging environmental stimuli, changes in myelinated and unmyelinated afferent fibers of nociceptive pathways and an increase in damage to those remaining. In part or in combination, these changes result in an overall slowing of information processing. In addition, dendritic arborization patterns change and neurofibrillary abnormalities are found throughout the aging brain and brainstem,
including in areas typically associated with nociceptive processing (Gibson & Farrell, 2004).

The impact of pain upon older adults is striking and is associated a broad range of both physical and psychosocial outcomes. In older adults, pain profoundly affects quality of life (Katz, 2002) and, if uncontrolled, is associated with depression, anxiety, falls, malnutrition, cognitive impairment, sleep abnormalities, functional disturbances, increasing health care expenditures, and decreased participation in social and recreational activities (Herr & Garand, 2001). The “gold standard” for chronic/severe pain relief continues to be opioid medications, but their analgesic power is as well known as their side effects, including respiratory depression, cognitive impairment, and motor discoordination. The search for efficacious pain medications with few side effects continues to be a laborious task with little success. As the population of older adults increases, pursuit of interventions that improve the efficacy of pain control without inducing additional interactions or side effects is of the utmost importance.

**Pain Comorbidities in Older Adults**

The pain experience among older adults is often complicated. The conditions of anxiety and depression are highly comorbid in both the general and older adult populations. Treatment of anxiety and depression led to the discovery of positive side effects of antidepressants, such as pain control. That is, many antidepressants are today used to treat chronic pain conditions such as migraines (Jackson et al., 2015) and neuropathic pain (Dworkin et al.). The mechanism by which serotonin (and other neurotransmitter drugs) medications address pain is not fully understood; however, drugs
that assist with blocking neurotransmitter reuptake or their breakdown are effective in controlling both depression and physical symptoms of pain (Sussman, 2003).

Neuroimaging of patients in pain and in those with depression show abnormalities of the limbic and prefrontal cortex (Blackburn-Munro, 2004), making a shared mechanism likely. Regulation of serotonin has been shown to cause disruption in the relationship between the PAG and HPA axis (Hestermann, Temel, Blokland, & Lim, 2014), indicating a close structural relationship. It is therefore understandable that serotonin/norepinephrine targeted medications are often effective in treatment of both pain and depressive conditions (Kaufman & Charney, 2000; QuickFacts, Louisiana, 2010). For example, amitriptyline, a serotonin-norepinephrine reuptake inhibitor, has been successfully used for many years to treat both anxiety and depression (Sindrup, Otto, Finnerup, & Jensen, 2005).

In general, manipulation of stress/anxiety/depression via antidepressants causes changes in learning and memory and, when decreased, also reduces complaints of pain (Tang & Gibson, 2005). Older adults are often prescribed antidepressants for pain control (Abdulla et al., 2013) and a high number of older adults experience comorbid depression and pain (Bonnecwyn et al., 2009). However, only 55% of those identified as depressed on the Minimum Data Set (MDS) received medication for this condition, and of those, 78% were under-medicated according to the manufacturers’ recommended minimum dose (Brown, Lapane, & Luisi, 2002). However, negative drug-drug interactions are a concern in older adults (Doucet et al., 1996). Polypharmacy (≥9 or more medications) dramatically increases cost, chance of side effects, falls (Maher, Hanlon, & Hajjar, 2014), morbidity and mortality (Hajjar, Cafiero, & Hanlon, 2007). This suggests that the need
for interventions that address both is critical. A substitute, then, could be a positive feedback loop that may mimic the conditions artificially created by antidepressants: establishing an environment that provides a boost in serotonin via occasions for control, positive engagement and opportunities for self-efficacy could increase available neurotransmitters in the same way as does medication.

**A BRIEF REVIEW OF COMPLEMENTARY MEDICINE**

**Environmental Enrichment and Complementary Medicine**

A promising strategy to help control pain originates from the theory of Environmental Enrichment (EE). In captive animals, EE has historically been considered a quality of life (QoL) issue; however, it continues to be studied with more scientific rigor and theoretical models for its efficacy constantly develop. Differences remain among vivariums and zoos and between species and objects, but EE in animals is usually considered to consist of 3 basic elements: social opportunities, exercise opportunities, and novel experiences. In general, studies with animals use the terminology *environmental enrichment*, while research studying the environment in humans uses terminology such as *sensory integration or complementary medicine*. Both, however, work with the impact environment has upon biological and psychosocial variables (Forssberg & Hirschfeld, 1992) (NCCAM, 2013). Only one study was found that discusses environmental manipulation with human subjects as “environmental enrichment” (Woo & Leon, 2013), and these scholars referenced the previous work of animal models as a rationale for their methodology. Because the impact of environment has been studied in both animal and human models, a variety of disciplines continue to study the benefits and risks associated with it and develop the theory as it moves forward.
In the social sciences, *built environment* refers to the mechanisms (including infrastructure and organizations) humans have erected to coordinate and function (Cunningham & Michael, 2004). In the EE context, this includes the environment to which older adults may transition in later life, or modifications made to their original homes to support aging (Cunningham & Michael, 2004). With onset of illness, changes may be made to the environment that provides appropriate stimulation for older adults (van Hoof, Kort, van Waarde, & Blom, 2010). Combined with the environmental stress theory of *information overload*, in which sources of stimulation (which may include elements of the built environment) such as change, novelty, complexity, intensity and inconsistency, may produce hyperstimulation and evoke a neurochemical stress response (Wingfield, 2013).

Enriching experiences in the older adult population have been shown to have positive effects across multiple measures. The 1987 Omnibus Budget Reconciliation Act (OBRA) included regulations which required all nursing care homes who receive Medicare and Medicaid monies to improve QoL and quality of care for their patients; nursing care facilities were to improve QoL by scheduling enrichment activities. While it is important to note the link between QoL and environment via organized activities, this provision was intended to address deficits in resident’s *quality of life* (Hawes et al., 1997); it was not intended to nor did it mention activity as a means of lowering pain report or of consumption of pain medication (Figure 1). Adding activities and therefore changing the environment to become more dynamic and energetic without considering the impact may exacerbate discomfort rather than ameliorating it (Wingfield, 2013). However, the use of complementary and alternative medicine (CAM) to treat a variety of
conditions, including pain, has recently begun to gain national momentum, and older adults are also participating in this trend (Morone & Greco, 2007; Yang, Decety, Lee, Chen, & Cheng, 2009). For many, the issue of understanding CAM remains in definition, clinical studies and documentation.

Table 1. U.S. Code 1396r. Requirements for Nursing Homes.

<table>
<thead>
<tr>
<th>(b) Requirements relating to provision of services</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Quality of life</td>
</tr>
<tr>
<td>(A) In general</td>
</tr>
<tr>
<td>A nursing facility must care for its residents in such a manner and in such an environment as will promote maintenance or enhancement of the quality of life of each resident.</td>
</tr>
<tr>
<td>(B) Quality assessment and assurance</td>
</tr>
<tr>
<td>A nursing facility must maintain a quality assessment and assurance committee, consisting of the director of nursing services, a physician designated by the facility, and at least 3 other members of the facility’s staff, which (i) meets at least quarterly to identify issues with respect to which quality assessment and assurance activities are necessary and (ii) develops and implements appropriate plans of action to correct identified quality deficiencies. A State or the Secretary may not require disclosure of the records of such committee except insofar as such disclosure is related to the compliance of such committee with the requirements of this subparagraph.</td>
</tr>
<tr>
<td>(2) Scope of services and activities under plan of care</td>
</tr>
<tr>
<td>A nursing facility must provide services and activities to attain or maintain the highest practicable physical, mental, and psychosocial well-being of each resident in accordance with a written plan of care which—</td>
</tr>
<tr>
<td>(A) describes the medical, nursing, and psychosocial needs of the resident and how such needs will be met;</td>
</tr>
<tr>
<td>(B) is initially prepared, with the participation to the extent practicable of the resident or the resident’s family or legal representative, by a team which includes the resident’s attending physician and a registered professional nurse with responsibility for the resident; and</td>
</tr>
<tr>
<td>(C) is periodically reviewed and revised by such team after each assessment under paragraph (3).</td>
</tr>
</tbody>
</table>

Creative Arts Therapies

Similar to CAM, the creative arts therapies have been shown to address and remediate a wide variety of symptoms affecting older adults. Among studies examining
music (Solé, Mercadal-Brotorns, Gallego, & Riera, 2010), art (McCaffrey, 2007), and movement therapy (Shimizu et al., 2013), all report improvements in healthy older adult populations. Music therapy has been shown to have a positive effect on quality of life and biomedical measures (blood pressure, muscle strength, pulmonary function, balance measures) in both well (Jeon, Kim, & Yoo, 2009) (Shimizu et al., 2013), and ill older adults (Wall & Duffy, 2010; Zare, Ebrahimi, & Birashk, 2010), including those at end of life (Hilliard, 2005; Krout, 2001). However, it is important to note that this is a therapeutic intervention rather than an enrichment.

Until recently, a great deal of effort has been involved in understanding and standardizing the therapeutic elements of creative therapies. Although the consensus is positive regarding creative arts therapies, these studies often lack standardization in methodology (Marshall & Hutchinson; Zhao, Bai, Bo, & Chi, 2016). That is, because artistic interventions are by definition dynamic, it is nearly impossible to guarantee that facilitators will use the same parameters in musical interventions, art supplies in visual arts interventions, and so on. Although qualitative research and personal accounts of these therapies’ efficacy had been published for decades, creative arts therapies continued to suffer from standardization and reproducibility inadequacies. Furthermore, the creative arts therapies were in general resistant to efforts to systematize assessment and treatment practices, and studies using creative arts therapies or creative interventions often used self-report health scales and therefore lack an objective, quantitative measure of analysis. Specifically, many practicing creative arts therapists feel the dynamic nature of arts therapies engenders flexibility in meeting client needs (Brooke, 2006), yet, reproducibility is one of the tenets of sound scientific research, and many therapists and
their professional organizations wanted creditability. Variability remains an unresolved issue in creative arts therapy research.

*Environmental Enrichment and Complementary and Alternative Medicine*

To the contrary, EE research may be and possibly should be “as sloppy as life itself” (Stine-Morrow, Parisi, Morrow, & Park, 2008) p. 786 *because* of the variability inherent in human personality, ability levels, artistic endeavors and success, etc. EE research has expanded the creative arts therapy model to investigate the contribution of several factors at once to the client outcome. For example, studying the impact of choir singing in a group of older adults (Johnson et al., 2013; Teater & Baldwin, 2014) rather than the impact of music therapy intervention on one participant, or examining the effect of general creative activities on health outcomes, such as the large study in Sweden, which found a positive relationship between attending cultural events and measures of physical health (Bygren, Konlaan, & Johansson, 1996). In studies such as these, the intervention is inherently non-standardized, because in a choir study an entire group of people cannot reproduce the same conditions every rehearsal (music, time of day, temperature in room, attendees, etc.), the events attended are not the same in a cultural participation study, the art is not the same at each viewing in a drawing class, and so on. With these parameters in mind, research continues to be conducted on both large and small scales and with a variety of populations and creative interventions.

Although both physicians and patients in many countries report using CAM approaches (Joos, Musselmann, & Szecsenyi, 2010) in healthcare, the definition of CAM remains broad. The National Center for Complementary and Alternative Medicine (NCCAM) acknowledges that defining CAM is difficult because of its broad applications
but asserts, “CAM is a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine” (NCCAM, 2013). These may include a wide variety of interventions including hypnosis, meditation and guided imagery, therapy, spiritual endeavors, and music (Bruckenthal, 2010). The NCCAM reminds its readers “Complementary medicine refers to use of CAM together with conventional medicine… to help lessen pain” (NCCAM, 2013). Indeed, Bruckenthal’s review (2010) of CAM found that pain was the most common reason older adults utilized CAM, and the NCCAM found 73% of respondents 50 years of age and older report pain control as the main reason CAM was utilized (NCCAM, 2013). Patients recovering in a room with more sunlight reported less stress and pain, required less opioid-equivalent medication (Walch et al., 2005) and stayed fewer days in the hospital (Beauchemin & Hays, 1996). Exposure to natural elements, whether views of nature or natural sounds, has been associated with a faster shift from strong to mild analgesics (Ulrich, 1984), expression of greater feelings of control over pain or self-efficacy (Lechtzin et al., 2010) and overall higher pain tolerance and thresholds (Tse, Ng, Chung, & Wong, 2002). In each of these scenarios, the environment was dynamic and involved a treatment team, further diversifying the patient experience and study parameters (Findlay, 2003).

In addition to self-efficacy and distraction, research has documented the contribution of social interaction to the pain experience and health outcomes. That is, loneliness or social isolation are a robust indicators of poor health outcomes, while higher feelings of being loved or being of value to others (known as social capital, see Chapter 1) predict better health outcomes (Cacioppo & Hawkley, 2009; N. Eisenberger & Cole,
Social support has been identified as a mediator in both pain and depressive symptoms (Ferreria & Sherman, 2007), and is considered to be supportive when the network is large and similar to the demographic makeup of the patient (Ashida & Heaney, 2008). That is, support is considered to be truly meaningful when the network is close in proximity, large in number, and similar demographically to the person needing it.

Interventions that facilitate interactive social experiences have been shown to improve health measures in older adults (Andersson, 1985), but those offering passive interaction between participants have had more limited success (Findlay, 2003). The difference seems to be that social isolation is an objective measure of time spent interacting with others, while loneliness is a subjective assessment of one’s personal experience of relationships. The literature has been mixed, with some researchers finding isolation has been associated with poor health outcomes (Steptoe, Shankar, Demakakos, & Wardle, 2013) and others attributing the decline to loneliness (Luo, Hawkley, Waite, & Cacioppo, 2012); however, the contribution of stable social networks to positive health outcomes has a robust literature.

While the exact mechanisms for the wide variety of improvements reported from CAM are not known, Cohen et al (2006) speculate one main mechanism may be the sense of control and/or self-mastery participation in the arts provides. In particular, Cohen’s group found older adults participating in socially engaging cultural activities took less medication than their control group counterparts. This is particularly relevant to our study, as growing evidence suggests the sense of control or self-efficacy has been implicated in the moderation of pain perception through both opioid and non-opioid
systems (Bandura, O'Leary, Taylor, Gauthier, & Gossard, 1987; Morone & Greco, 2007; Wasan, Davar, & Jamison, 2005) and this points to a role for regular engagement in activities in older adulthood. This was confirmed by Everitt and Hamilton (2003), These authors suggest that community arts programs are able to address health in a holistic manner, crossing & breaking boundaries held fast by traditional health agencies. The role of socialization in pain modulation is also becoming more apparent, with studies proving the presence of a supportive social network to attenuate pain perception (Cano, Johansen, & Geisser, 2004; Coan, Schaefer, & Davidson, 2006; McGrath, 1994).

Through the combination of social interaction and changing environments, EE engenders a “sense of control and self-confidence” (Patterson & Perlstein, 2011) p. 28 one cannot experience in an isolated, stagnant environment. This sense of control is also known as self-efficacy, and has been correlated with decreased perception of pain and consumption of pain medication (Manning & Wright, 1983). Improved self-efficacy and autonomy leads to greater ability to self-advocate, decreased physiological processes that draw attention to pain sensations (Bandura, Reese, & Adams, 1982), creates a positive loop regarding physical activity (Shoor & Holman, 1984) and, leads to overall decreased mortality (Vaananen et al., 2009). Low self-efficacy is a strong predictor of both disability and pain intensity (Arnstein, Caudill, Mandle, Norris, & Beasley, 1999).

**CAM as treatment**

Although research has been strong in support of EE in animals and humans, the adoption of it as an intervention has been slow. Prior to development of the Omnibus Budget Reconciliation Act (OBRA) of 1987, many inconsistencies existed in nursing home practice and documentation, ranging from overuse of physical restraints to
inadequate psychosocial and behavior management habits. The Minimum Data Set (MDS) is the assessment tool introduced in the OBRA to rectify these irregularities and is now required by nursing homes caring for Medicaid and Medicare patients. Importantly, the MDS was intended to “focus on identifying treatable, reversible causes of functional limitations and on restoring and maintaining function” (Hawes et al., 1997, p. 978) -- EE has been shown to address each of these issues.

The MDS was first developed in 1988 and implemented nationally in the fall of 1996 (Reinhard, Hendrickson, & Bemis, 2005), and updates are occasionally released. The MDS does not contain a consistent pain rating scale to collect patient pain report; rather, the pain scale is different for each variable (some binary, some continuous). The MDS has been shown to be valid and reliable in general (Fries, Simon, Morris, Flodstrom, & Bookstein, 2001; Hawes et al., 1995; Landi et al., 2000) and more specifically, in both community-dwelling adults and those in nursing homes (Morris et al., 1997).

One major criticism in the original MDS was lack of attention to QOL issues; although the MDS discussed QOL, an official QOL data collection section was not included (Services, 2006). Numerous studies indicate the MDS is an excellent predictor for biomedical events such as mortality and hospitalization (Rahman & Applebaum, 2009) but no QOL section has been added. In fact, the MDS 3.0 has entirely replaced the psychosocial domain with questions regarding patient preferences, using these answers as a kind of proxy for QOL interpretation (Rahman & Applebaum, 2009). We have attempted to remove the problem of interpretation by using the questions in section F (A)
(Length of time client is alone during the day) and (B) (Client says or indicates that he/she feels lonely) simply as markers of their content.

**Program for All Inclusive Care for the Elderly (PACE)**

The Program for All Inclusive Care for the Elderly (PACE) is a model of incorporating EE into healthcare for older adults. PACE began in the 1970s in San Francisco’s Chinatown. Although many elderly residents with strong foreign-culture identities (recent immigrants, naturalized, and natural-born citizens) were appropriate for facility care, this was not a culturally accepted option, leaving these adults vulnerable to safety concerns and lacking in systematic, organized care. A community-based task force opened one of the first adult day health centers in San Francisco in 1973. After a successful year providing services to its participants, the first PACE program received Medicaid funding in 1973 and soon after expanded services to include in-home care, meals & housing assistance. Today there are 116 PACE programs in 32 states, and PACE continues to demonstrate that this interdisciplinary approach to aging is efficacious and cost-effective (Hirth, Baskins, & Dever-Bumba, 2009).

The PACE program aims to keep elders residing in the community, and ideally residing in their own homes, as long as possible. At the core of the PACE model is the adult day center (Dana B. Mukamel et al., 2007). To this end, this model provides medical care, prescription medications, rehabilitation services such as speech and occupational therapy, meals, laboratory and x-ray services, counseling, respite care, transportation to medical appointments, medical equipment, and adult day health care. Transportation is provided to and from the day center, at which are rehabilitation therapies, personal care, pastoral and social services, nutritional counseling, primary and
specialty medical appointments, meals, and activities. Additional in-home services include in-home care, caregiver/respite support, modifications to the home as needed, medical supplies and equipment, and hospitalization/nursing care. Activities (crafts, games) and services (music therapy, pet therapy) may be offered at specific locations depending upon availability and individual contracts. These services are capitated, meaning the fee is the same for all patients regardless of service consumption and the fee is dependent upon a patient’s Medicare or Medicaid eligibility.

The New Orleans area PACE program offers a variety of services. Like other healthcare models, PACE is a model of comprehensive care, but the main PACE difference is the adult day health center and the interdisciplinary team (D. B. Mukamel et al., 2006), which may include up to 50 staff members. Mukamel et al (D. B. Mukamel et al., 2006) found that the more professionals involved in an individual’s care, the better the patient’s functional outcome. This indicates more professional assessment being delivered and also suggests increased interaction with a greater number of people and opportunities for activity per patient. In this way, PACE is a model of successful EE within comprehensive care.

As of 2012, Louisiana was among the states with the highest number of opioid prescriptions (Prevention, 2012). CAM research has proven the efficacy of its intervention in several domains; however, no specific recommendation for enriching activities with older adults exists. The purpose of this research was to determine the effect of an enriched environment upon pain perception and control, as well as to identify any relationship between changes in pain variables and their associated variables (loneliness, isolation) and changes in services over time.
Sources of data & original data collection process

These primary data were mined from one PACE center located in the Bywater area of New Orleans. At the time of data collection, the average daily census at this facility was 165. The Bywater neighborhood is one of the oldest areas of the city and has traditionally retained its residents from birth through death. However, in 2005, Hurricane Katrina struck the city of New Orleans and dramatically altered the population and demographics of the Bywater. Those who have returned have struggled to regain property ownership due to several factors. First, property in this and other areas of New Orleans were typically “heir properties”, meaning property was passed through the family from one generation to another. Although property taxes were paid and homes maintained, they were not listed as property owners and, therefore, could not receive federal assistance money (Appleseed, 2013). In 2000, occupied housing units in the Bywater were 83%; by 2010 it had recovered to only 70.6%. Secondly, vacant housing units had almost doubled between 2000 and 2010, from 17% to 29.4%. Additionally, the number of older adults (50 years old and over, as defined by the data source) in 2010 was 25% of the Bywater population; by 2010 it rose to 32.1% (Center, 2015). The large number of vacant housing units and shifting demographics create safety concerns that make procuring a prescription for opioids even less desirable, producing the perfect opportunity for EE to assist with pain control and quality of life in the safety of an organized facility such as PACE.

Original Data Collection Process

The MDS (see Table 11) is administered to all patients upon admission to the PACE program. Following the MDS, a Registered Nurse (RN) collects data from the
participant and family and enters information into the electronic medical record. As mentioned above, the MDS is a rich and extensive assessment tool and includes biomedical and psychosocial data, medications, and quality of life measures. The MDS is re-administered every six months or upon a significant change in status (hospitalization, new diagnosis, etc.).

**Sample Demographics**

This PACE sample used in this study was predominantly non-Hispanic African American. The racial makeup was 7.57% White or White, not of Hispanic origin, 2.72% Hispanic, and 91.66% Black or African American/Black, not of Hispanic Origin. For this analysis data were collapsed into the categories of Black/African-American/not of Hispanic Origin, White/not of Hispanic Origin, and Hispanic (Table 2).

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Sample</th>
<th>% of Whole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 50-59</td>
<td>4</td>
<td>3.07</td>
</tr>
<tr>
<td>Ages 60-69</td>
<td>46</td>
<td>35.38</td>
</tr>
<tr>
<td>Ages 70-79</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>Ages 80-89</td>
<td>36</td>
<td>27.69</td>
</tr>
<tr>
<td>Ages 90-99</td>
<td>18</td>
<td>15.38</td>
</tr>
<tr>
<td>Age 100+</td>
<td>1</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean Age</td>
<td>76.36</td>
<td>N/A</td>
</tr>
<tr>
<td>Men</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Women</td>
<td>101</td>
<td>78</td>
</tr>
<tr>
<td>African-American</td>
<td>127</td>
<td>91.66</td>
</tr>
<tr>
<td>White</td>
<td>10</td>
<td>7.57</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
<td>2.72</td>
</tr>
</tbody>
</table>

According to the 2010 United States Census Bureau, the population of older adults (65 years and older) living in New Orleans was 10.9% of the city’s population, compared to Louisiana’s 12.3% and the United States 13%. In the city of New Orleans, those adults identifying as Black or African American was determined to be 60.2%, those reporting as White was 33%, Asians represented 2.9%, and those identifying as Hispanic was 5.2%; the remaining difference is comprised of very small representations or of those identifying with two or more races. The 2010 New Orleans
population (Table 3) included a total of 51.6% females and 49.4% males; the population of Louisiana was 51% female and 49% male in 2010 (QuickFacts, Louisiana, 2010).

**Data Included in the Sample**
In this study, data from the first and last MDS were included. Data were not stratified by length of time in the PACE program; rather, admit (first) MDS and most recent (last) MDS were used as pre- and post- tests. Outcome variables were pain frequency, pain intensity, isolation, loneliness, number of medications, medication type, and feeling that medications controlled pain adequately. Control variables were age, race, and sex.

Table 3. Selected demographics of the United States, Louisiana, New Orleans, and PACE New Orleans. All numbers in percentage.

<table>
<thead>
<tr>
<th>2010 Census</th>
<th>United States</th>
<th>Louisiana</th>
<th>New Orleans</th>
<th>PACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50.8</td>
<td>51</td>
<td>51.6</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>49.2</td>
<td>49</td>
<td>48.4</td>
<td>80</td>
</tr>
<tr>
<td>Black or African</td>
<td>12.6</td>
<td>32.0</td>
<td>60.2</td>
<td>92.03</td>
</tr>
<tr>
<td>White</td>
<td>77.4</td>
<td>62.6</td>
<td>33</td>
<td>6.17</td>
</tr>
<tr>
<td>Asians</td>
<td>4.8</td>
<td>1.5</td>
<td>2.9</td>
<td>N/A</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.3</td>
<td>4.2</td>
<td>5.2</td>
<td>1.24</td>
</tr>
</tbody>
</table>

**Hypotheses**

**Hypothesis 1** Pain is lower in participants who use any combination of services that include PACE;

1.1 Pain intensity is lower in participants who use any combination of services that include PACE day program;

1.2 Pain frequency is higher in participants who use any combination of services that include PACE day program.

**Hypothesis 2**: Loneliness and isolation are lower in participants who attend any combination of the PACE day program;
Hypothesis 3: Medication-associated variables are lower in those participants who use any combination of services that include the PACE day program;

3.1 Number a of medications is lower in participants who use any combination of services that include the PACE day program;
3.2 Complexity of medications is lower in participants who use any combination of services that include the PACE day program;
3.3 Pain controlled by medication scores are higher in participants who use any combination of services that include the PACE day program

Hypothesis 4: Positive changes in pain intensity, frequency, and pain control, number of medications and medication type from Time 1 to Time 2 are associated with change in services that reflect greater PACE day program attendance was rejected.

4.1 Change in pain intensity is related to addition of PACE services;
4.2 Change in pain frequency is related to addition of PACE services;
4.3 Feelings of pain control are related to addition of PACE services;
4.4 Change in medication type is related to addition to PACE services.

Analysis Plan
Thirty-one patients had only one MDS record (admission) and were therefore not appropriate for a repeated measures analysis. This sample had a remarkably low occurrence of missing values with very few files containing consistently missing data, bringing the total number of files analyzed to 130. Data were analyzed using Statistical
Program for the Social Sciences, (SPSS; IBM) version 23. Data were analyzed by one-way analysis of variance (ANOVA) and, if significant, a Tukey Honest Significant Difference (HSD) was employed post-hoc to determine groups responsible and at what significance level. Data collected by the MDS-HC are provided below (Table 4):

Table 4. Minimum Data Set (MDS) Sections & Questions.

<table>
<thead>
<tr>
<th>MDS Section Question</th>
<th>Name</th>
<th>Variable Name</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section F, Question 3a</td>
<td>Social Functioning: Isolation</td>
<td>Isolation 1 &amp; 2</td>
<td>Length of time client is alone during the day (morning and afternoon):</td>
<td>0. Never or hardly ever</td>
</tr>
<tr>
<td>Section F, Question 3b</td>
<td>Social Functioning: Isolation</td>
<td>Lonely 1 &amp; 2</td>
<td>Client says or indicates that he/she feels lonely</td>
<td>0. No</td>
</tr>
<tr>
<td>Section K, Question 4a</td>
<td>Health Conditions and Preventive Health Measures: Pain</td>
<td>Pain Frequency 1 &amp; 2</td>
<td>Frequency with which client complains or shows evidence of pain:</td>
<td>0. No pain</td>
</tr>
<tr>
<td>Section K, Question 4b</td>
<td>Health Conditions and Preventive Health Measures: Pain</td>
<td>Pain Intensity 1 &amp; 2</td>
<td>Intensity of pain</td>
<td>0. No pain</td>
</tr>
<tr>
<td>Section K, Question 4e</td>
<td>Health Conditions and Preventive Health Measures: Pain</td>
<td>Pain Controlled 1 &amp; 2</td>
<td>From client’s point of view, medications adequately control pain</td>
<td>0. Yes or no pain</td>
</tr>
</tbody>
</table>
### VARIABLES

All variables had a pre (Time 1) and post (Time 2) score.

**Pain**

Pain frequency, intensity coding was transferred directly from the MDS (see Table 4).


**Services**

PACE offers a wide diversity of services to its participants. These may be full or part-time attendance at a day program and also in-home visits from a variety of professionals and volunteers such as home health aides, nurses, occupation, physical and speech therapists, social workers, and homemaking assistants. To simplify this assortment, activities were sorted into 4 categories (Table 5). Additionally, as stated in the table below, it is important to note that in this analysis, numerical increases in coding reflects increases in services and therefore EE. Additionally, “PACE” in this context means the *PACE day program*, while Only Others means *receives some in-home services* (Registered Nurse, Social Worker, Physical Therapy, etc.), and PACE Combo means *only attends the PACE day program OR attends the PACE day program AND receives in-home services*. That is, groups of adults in the “only others” category may have continued to work, keep medical appointments, maintain regular rehabilitation services elsewhere; however, these services did not take place in the home and were presumed to be routine and predictable in nature. The variables of age, race, and sex were assigned a binary code and were controlled for in each analysis. When referring to the PACE philosophy and its interventions as a whole, we use the terminology, “PACE program.”

**Table 5. Coding of Service Utilization Variable.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Service Category</th>
<th>Coding Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Attends no day program, receives no in-home services</td>
</tr>
<tr>
<td>2</td>
<td>Only Others</td>
<td>Receives only in-home services</td>
</tr>
<tr>
<td>3</td>
<td>PACE Combo</td>
<td>Attends PACE day program or attends day program and receives in-home services</td>
</tr>
</tbody>
</table>
Medications

Coding of medications was simplified due to the wide variety of medications prescribed in this sample. A very small number of patients were prescribed medications for psychiatric diagnoses or anticonvulsants for seizure disorders. Further, especially in MDS-HC Time 1 data, suspected or confirmed diagnosis of dementia was often simultaneously recorded as a psychiatric illness. For this reason, medication was a better indicator of psychiatric diagnoses/illness than was Section J, Disease, of the MDSHC. Antidepressants are often prescribed for pain control and anticonvulsants are now considered an excellent treatment for chronic pain (Maizels & McCarberg, 2005); therefore, antidepressants and anticonvulsants were coded as pain preventives unless a psychiatric diagnosis was specified in the medical record. Medication types were simplified into 9 categories, and most participants fell easily into these categories (Table 6). Medications such as acetaminophen or naproxen sodium available without a prescription were coded as over the counter (OTC), prescription pain medications that could be taken either as needed or scheduled such as hydrocodone were coded as pain medication and medications commonly used for pain prevention in patients who did not have the diagnoses for which these medicines were otherwise prescribed (for example, an anticonvulsant is listed but the patient does not have a seizure disorder or history of convulsions) were coded as preventive (Table 7). Because our study’s purpose was to examine the impact services had upon pain variables including medication, participants taking no medication were coded as missing and excluded from the analysis.

Table 6. Descriptive Statistics of Medication Type Variable.

<table>
<thead>
<tr>
<th>Med Type</th>
<th>Count / % of Svcs1</th>
<th>None</th>
<th>Only Others</th>
<th>PACE Combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>None for Pain</td>
<td>15/19.20</td>
<td>4/11.10</td>
<td>4/0.156</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Med Type</td>
<td>Count / % of Svcs1</td>
<td>Count / % of Svcs2</td>
<td>Count / % of Svcs1</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1</td>
<td>OTC Only</td>
<td>29/37.2</td>
<td>10/58.8</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds Only</td>
<td>7/9.0</td>
<td>1/17.6</td>
<td>7/9.0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + OTC</td>
<td>7/9.0</td>
<td>1/17.6</td>
<td>10/0.376</td>
</tr>
<tr>
<td></td>
<td>Preventive Only</td>
<td>2/2.6</td>
<td>2/10.0</td>
<td>3/0.124</td>
</tr>
<tr>
<td></td>
<td>OTC + Preventive</td>
<td>11/14.1</td>
<td>4/11.1</td>
<td>5/0.294</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + Preventive</td>
<td>2/2.6</td>
<td>1/2.8</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + OTC + Preventive</td>
<td>5/6.4</td>
<td>3/8.3</td>
<td>5/0.215</td>
</tr>
<tr>
<td></td>
<td>No Meds Prescribed</td>
<td>0/0</td>
<td>1/2.8</td>
<td>0/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Med Type</th>
<th>Count / % of Svcs1</th>
<th>Count / % of Svcs2</th>
<th>Count / % of Svcs1</th>
<th>Count / % of Svcs2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>OTC Only</td>
<td>1/5.9</td>
<td>1/2.8</td>
<td>1/5.9</td>
<td>1/2.8</td>
</tr>
<tr>
<td></td>
<td>Pain Meds Only</td>
<td>0/0</td>
<td>2/10.0</td>
<td>10/0.199</td>
<td>2/10.0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + OTC</td>
<td>1/5.9</td>
<td>1/5.0</td>
<td>6/0.168</td>
<td>1/5.0</td>
</tr>
<tr>
<td></td>
<td>Preventive Only</td>
<td>0/0</td>
<td>2/10.0</td>
<td>4/0.085</td>
<td>2/10.0</td>
</tr>
<tr>
<td></td>
<td>OTC + Preventive</td>
<td>3/17.6</td>
<td>0/0</td>
<td>8/0.116</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + Preventive</td>
<td>0/0</td>
<td>1/5.0</td>
<td>2/0.056</td>
<td>1/5.0</td>
</tr>
<tr>
<td></td>
<td>Pain Meds + OTC + Preventive</td>
<td>0/0</td>
<td>0/0</td>
<td>2/0.029</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>No Meds Prescribed</td>
<td>0/0</td>
<td>1/5.0</td>
<td>2/0.029</td>
<td>1/5.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Med Code</th>
<th>Medications listed</th>
<th>Coding Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None for pain</td>
<td>No medications prescribed for pain</td>
</tr>
<tr>
<td>2</td>
<td>OTC only</td>
<td>Only over the Counter medications for pain listed</td>
</tr>
<tr>
<td>3</td>
<td>Pain Meds Only</td>
<td>Only prescription pain medications listed</td>
</tr>
<tr>
<td>4</td>
<td>Pain Meds + OTC</td>
<td>Prescription pain medications and over the counter</td>
</tr>
</tbody>
</table>
Control Variables

Sex, Race, and Age were analyzed in a previous separate analysis (repeated measures ANOVA), and no statistical significance was found between any control variable and any outcome variable. Based upon the preliminary results from this analysis, data were analyzed using the one-way ANOVA statistical design, as it is more appropriate for these data.

Change Scoring

To create the change variables (pain intensity change, pain frequency change, pain control change, isolation change, loneliness change, services change, and medication type and number of medications change), the difference in scores, Time 1, was subtracted from Time 2 and a new variable was created. The results, therefore, appear are “Decreased by 1, Increased by 2”, etc. For example, if at Time 1, a participant was consuming no services (score of 1) but changed to PACE Combo by Time 2 (score of 3), that participant’s score would be “Increased by 2”. The scores were linked to the original participant codes to maintain the tracking system for overall picture of patient pain and socialization variables. RESULTS

<table>
<thead>
<tr>
<th>No.</th>
<th>Pain Medications Listed</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Preventive Meds Only</td>
</tr>
<tr>
<td>6</td>
<td>OTC + Preventive</td>
</tr>
<tr>
<td>7</td>
<td>Pain Meds + Preventive</td>
</tr>
<tr>
<td>8</td>
<td>Pain Meds + Preventive + OTC</td>
</tr>
<tr>
<td>9</td>
<td>No Meds Prescribed</td>
</tr>
</tbody>
</table>

- 5: Preventive Meds Only: Only prescription preventive medications listed
- 6: OTC + Preventive: Over the counter and preventive pain medications listed
- 7: Pain Meds + Preventive: Pain medications and preventive pain medications listed
- 8: Pain Meds + Preventive + OTC: Pain medications, preventive pain medications and over the counter pain medications listed
- 9: No Meds Prescribed: No pain medications listed (missing)
**All variables, pre & post**

A paired-samples t-test was used to detect differences between first and last MDS administered (Table 8). Statistically significant differences were found in services, pain intensity, pain frequency, number and type of medications, and patient assessment of adequate control of pain by medication. For all analyses, statistical significance is reached at *p*≤0.05, **p*≤0.01, ***p*≤0.001, and trending significance were scores p≤0.10.

**Table 8. T-tests of all variables, Time 1 - Time 2.**

<table>
<thead>
<tr>
<th></th>
<th>Variable</th>
<th>Time 1 Mean/ st. dev.</th>
<th>Time 2 Mean/ st. dev.</th>
<th>Mean Difference</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pain Intensity**</td>
<td>1.8175/1.504</td>
<td>1.4206/1.39</td>
<td>0.39683</td>
<td>2.828</td>
<td>0.005</td>
</tr>
<tr>
<td>2</td>
<td>Pain Frequency *</td>
<td>1.3095/1.255</td>
<td>1.5952/1.25</td>
<td>0.2857</td>
<td>2.092</td>
<td>0.038</td>
</tr>
<tr>
<td>3</td>
<td>Isolation</td>
<td>0.7619/0.958</td>
<td>0.7619/0.98</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>Loneliness</td>
<td>0.55/0.5</td>
<td>0.4683/0.50</td>
<td>0.7937</td>
<td>1.365</td>
<td>0.175</td>
</tr>
<tr>
<td>5</td>
<td>Number of Medications ***</td>
<td>12.2619/4.85</td>
<td>8.02384.620</td>
<td>4.2381</td>
<td>10.115</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>Medication Type ***</td>
<td>3.4127/2.147</td>
<td>2.5079/1.83</td>
<td>0.90476</td>
<td>4.625</td>
<td>0.001</td>
</tr>
<tr>
<td>7</td>
<td>Pain Controlled by Medications **</td>
<td>0.6032/0.705</td>
<td>0.3889/0.66</td>
<td>0.2143</td>
<td>2.505</td>
<td>0.014</td>
</tr>
<tr>
<td>8</td>
<td>Services **</td>
<td>2.57940.719</td>
<td>1.9048/0.88</td>
<td>0.67460</td>
<td>6.921</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**All variables, pre-tests**

**Table 9. Results of One-way ANOVA, Time 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Intensity 1</td>
<td>(2,126)</td>
<td>1.895</td>
<td>0.155</td>
</tr>
<tr>
<td>Pain Frequency 1</td>
<td>(2, 126)</td>
<td>1.236</td>
<td>0.294</td>
</tr>
<tr>
<td>Isolated 1</td>
<td>(2, 126)</td>
<td>0.437</td>
<td>0.647</td>
</tr>
</tbody>
</table>
One-way ANOVAs were run to compare key pain across different service groups, i.e., no-services group ("None"), other-services group ("Only Others"), and day-center group ("PACE Combo"). The first ANOVA (Table 9, Time 1) detected no significant or trending differences in any variables. The second ANOVA (Table 10, Time 2) detected statistically significant differences at Time 2 in pain intensity, pain frequency, and pain controlled by medication. Loneliness, number of medications, and medication type were not significant.

### Pain Intensity

Via one-way ANOVA, hypothesis 1.1, “**pain intensity is lower in adults who attend any combination of services that include the PACE day program**”, was
accepted. There was a statistically significant difference in pain intensity at Time 2, and this difference was between adults who engaged no PACE services (“None”) and those who attended the PACE day program (“PACE Combo”), F (2, 124) = 3.074 p≤0.04.

Table 11 shows the number of participants in each group, means and standard deviations at Time 1 and Time 2. Figure 15 is a visual representation of pain intensity in all groups, Time 1- Time 2.

Table 11. Pain Intensity x Service Group, Times 1 & 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Svc. Group</th>
<th>n</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PainIntensity1</td>
<td>None</td>
<td>17</td>
<td>1.2941</td>
<td>1.3585</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>2.25</td>
<td>1.5852</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>1.8140</td>
<td>1.4988</td>
</tr>
<tr>
<td>PainIntensity2</td>
<td>None</td>
<td>56</td>
<td>1.6964</td>
<td>1.6283</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>1.5185</td>
<td>1.0514</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>1.4252</td>
<td>1.3888</td>
</tr>
</tbody>
</table>
Figure 14. Pain Intensity Means, Standard Deviations, and Differences by Service Groups. Pain intensity declined in adults receiving in-home services and attending PACE day center but rose in adults receiving/participating in neither.

### Pain Frequency

**Hypothesis 1.2** “Pain frequency is lower in participants who attend any combination of services that include the PACE day program,” was rejected based on results of a one-way ANOVA. There was a statistically significant difference between groups of adults who consumed no PACE services (“None”) and those adults who engaged in-home services only ("Only Others"), with the “None” reporting a mean difference of 0.7103, p≤0.04. No control variables (race, sex, age) were significant in the pain frequency analysis. Table 12 shows the pain frequency number of participants in each group, means and standard deviations at Time 1 and Time 2. Figure 16 is a visual representation of pain intensity in all groups, Time 1- Time 2.
Table 12. Pain Frequency by Service Group, Times 1 & 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Svc. Group</th>
<th>n</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PainFrequency1</td>
<td>None</td>
<td>17</td>
<td>0.8824</td>
<td>1.2187</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>1.5000</td>
<td>1.2773</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>1.3261</td>
<td>1.2413</td>
</tr>
<tr>
<td>PainFrequency2</td>
<td>None</td>
<td>56</td>
<td>1.8214</td>
<td>1.2226</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>1.1111</td>
<td>1.2195</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>1.5683</td>
<td>1.2627</td>
</tr>
</tbody>
</table>

Figure 15. Pain Frequency Means, Standard Deviations, and Mean Differences by Service Groups. Pain frequency rose in adults receiving no services and attending the PACE day center, but declined in those receiving in-home services only.

Loneliness & Isolation

Hypothesis 2, "Loneliness and isolation are lower in participants who consume any combination of services which include the PACE day program", was rejected. In particular, from Time 1 - Time 2, loneliness decreased the most in participants who received in-home services (not those who attended the day program), followed by the PACE Combo group and finally rose slightly in the "None" group-participants engaging in no PACE services. Isolation, however, decreased the most from
Time 1 - Time 2 in the PACE Combo group, followed by the "Only Others" and rose in the "None" group. Table 13 shows the number of participants in each group, means and standard deviations at Time 1 and Time 2. Figure 17 is a visual representation of loneliness in all groups, Time 1 - Time 2. Figure 18 is a visual representation of isolation scores in all groups, Time 1 - Time 2.
Table 13. Loneliness & Isolation Means and Standard Deviations, Times 1 & 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Svc. Group</th>
<th>n</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonely1</td>
<td>None</td>
<td>17</td>
<td>0.4700</td>
<td>0.514</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>0.6000</td>
<td>0.503</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>0.5500</td>
<td>0.500</td>
</tr>
<tr>
<td>Lonely2</td>
<td>None</td>
<td>56</td>
<td>0.5000</td>
<td>0.5045</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>0.4444</td>
<td>0.5064</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>0.4318</td>
<td>0.5011</td>
</tr>
<tr>
<td>Isolated 1</td>
<td>None</td>
<td>56</td>
<td>0.8824</td>
<td>1.0537</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>0.9000</td>
<td>1.0711</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>0.7174</td>
<td>0.9178</td>
</tr>
<tr>
<td>Isolated2</td>
<td>None</td>
<td>56</td>
<td>0.9643</td>
<td>1.0438</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>0.8519</td>
<td>0.9885</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>0.4773</td>
<td>0.8488</td>
</tr>
</tbody>
</table>

Figure 16. Loneliness Means, Standard Deviations, and Mean Differences by Service Groups. Loneliness declined in participants utilizing PACE day center and in-home services but rose in those receiving no PACE services.
Figure 17. Isolation Means, Standard Deviations, and Mean Differences by Service Groups. Isolation declined only in participants attending the PACE day center.

Medication and Medication-Related Variables

Hypothesis 3.1, "Number of medications is lower in participants who use any services that include the PACE day program," was rejected, F (2, 124) = 1.180, p≤0.311. Hypothesis 3.2, "Complexity of medications is lower in participants who use any combination of services that include the PACE day program," was rejected. Although the difference between Times 1 & 2 was significant [F (2,124) = 3.195, p≤0.044], the Tukey HSD post-hoc tests revealed the significant difference was between the "None" and "Only Others" groups, mean difference in favor of "Only Others" - 1.0410, p≤0.043. Hypothesis 3.3, "Pain controlled by medication scores are higher in participants who attend any combination of services that include the PACE day program," was rejected, F (2, 124) = 2.906, p≤0.055. Because it was trending toward significance, a Tukey HSD analysis was also performed, and the groups responsible for the largest difference were the None vs. PACE Combo groups, mean difference 0.2955 in
favor of the PACE Combo group (pain controlled by medications is higher), \( p \leq 0.078 \).

Table 14 shows participants in each groups for all variables addressed in hypothesis 2;

Figure 19 is a visual representation of medication and medication-related variables, Time 1 - Time 2.

**Table 14. Medication and Medication-Related Variable Means and Standard Deviations, Time 1 & 2.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Svc. Group</th>
<th>n</th>
<th>Mean</th>
<th>Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Meds 1</td>
<td>None</td>
<td>17</td>
<td>10.2941</td>
<td>4.2686</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>13.000</td>
<td>5.6475</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>12.3478</td>
<td>4.7357</td>
</tr>
<tr>
<td>Number of Meds 2</td>
<td>None</td>
<td>56</td>
<td>7.3750</td>
<td>4.8899</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>8.9259</td>
<td>4.4629</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>8.3409</td>
<td>4.2860</td>
</tr>
<tr>
<td>Medication Type 1</td>
<td>None</td>
<td>17</td>
<td>2.8824</td>
<td>2.1176</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>3.0500</td>
<td>2.1392</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>3.5870</td>
<td>2.1440</td>
</tr>
<tr>
<td>Medication Type 2</td>
<td>None</td>
<td>56</td>
<td>2.1071</td>
<td>1.5803</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>3.1481</td>
<td>2.0885</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>2.6818</td>
<td>1.9502</td>
</tr>
<tr>
<td>Pain Controlled by Meds 1</td>
<td>None</td>
<td>17</td>
<td>0.3529</td>
<td>0.7019</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>20</td>
<td>0.6500</td>
<td>0.7412</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>92</td>
<td>0.6522</td>
<td>0.7022</td>
</tr>
<tr>
<td>Pain Controlled by Meds 2</td>
<td>None</td>
<td>56</td>
<td>0.5000</td>
<td>0.7386</td>
</tr>
<tr>
<td></td>
<td>Only Others</td>
<td>27</td>
<td>0.5185</td>
<td>0.8490</td>
</tr>
<tr>
<td></td>
<td>PACE Combo</td>
<td>44</td>
<td>0.2045</td>
<td>0.4080</td>
</tr>
</tbody>
</table>
Change Analyses

Hypothesis 4: Positive changes in pain intensity, frequency, and pain control, number of medications and medication type from Time 1 to Time 2 are associated with change in services that reflect greater PACE day program attendance was rejected, as were all more specific hypotheses (change in pain intensity, pain frequency, pain control, and medication variables.)

Table 15. Results of a One-way ANOVA of Outcomes Variable Change x Service Change.

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>F score</th>
<th>Sig.</th>
<th>Groups Mostly Responsible</th>
<th>Mean Difference</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Intensity Change</td>
<td>(4,125)</td>
<td>0.347</td>
<td>Increased by 1 vs. No Change</td>
<td>-0.73226</td>
<td>0.261</td>
</tr>
<tr>
<td>Pain Frequency Change</td>
<td>(4,125)</td>
<td>0.414</td>
<td>Decreased by 1 vs. Increased by 1</td>
<td>1.09668</td>
<td>0.497</td>
</tr>
<tr>
<td>Pain Control Change</td>
<td>(4,125)</td>
<td>0.306</td>
<td>No Change vs. Increased by 1</td>
<td>0.44903</td>
<td>0.255</td>
</tr>
<tr>
<td>Isolation Change</td>
<td>(4,105)</td>
<td>0.031</td>
<td>No Change vs. Increased by 1</td>
<td>0.71429</td>
<td>0.029</td>
</tr>
<tr>
<td>Loneliness</td>
<td>(4,125)</td>
<td>0.241</td>
<td>Decreased by 1 vs.</td>
<td>0.9346</td>
<td>0.353</td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td>Decreased by 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----</td>
<td>----------------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>Medication Type</td>
<td></td>
<td>Decreased by 2 vs. Increased by 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td>(4, 125) 0.958</td>
<td>0.433</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Meds</td>
<td></td>
<td>Decreased by 2 vs. No Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td>(4, 125) 0.526</td>
<td>0.717</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results from one-way ANOVA analysis for changes in the pain (intensity, frequency) x change in services and change in loneliness x change in services were non-significant (Table 15); however, change in HSD was employed post-hoc, revealing the groups responsible were the groups who made no changes in services (“No Change”) consumption and those who increased services by 1 service type (for example, going from “None” [no PACE services, code 1] to “PACE Combo” [attends day program, code 3] = increased by 2). The “no change” group experienced a higher mean isolation score of 0.7143, p ≤ 0.029 Because data were coded to reflect changes in PACE attendance to be positive in value, increases in services generally reflect more interaction and activity while decrease in services value reflects diminished activity and engagement with others. As results of the original ANOVA were not fully significant, post-hoc scores to determine between group differences were most often marginally significant as well. All results and most powerful pairwise comparisons are included in table 18, even when not statistically significant.

The complete Picture: Variables by Group
For ease of viewing, we have grouped together pain, medication, and psychosocial variables, followed by changes in services.

**Pain variables**
In the PACE Combo group, pain intensity decreased while pain frequency simultaneously increased. The group of participants who received services only in their
homes (“Only others”) declined in both pain intensity and frequency; the group who engaged no services at all rose in both (Figure 20). Self-efficacy may explain these differences: as participation in activity increases, there are inherently more opportunities to both encounter and evoke discomfort, but the distraction, sense of accomplishment and decreased fear when encountering novel experiences (Woby, Urmston, & Watson) may influence pain.

![Graph of Pain Variables by Service Group](image)

**Figure 19. Pain Variables by Service Group.**

**Medication variables**

Participants in the PACE Combo group saw a reduction in the number of medication as well as their complexity (Figure 12A); however, by Time 2 this group also took the most of the mildest pain medication (Table 6), followed only by those adults consuming no services. At Time 2, the number of respondents in the PACE Combo group who reported their pain was controlled or had no pain was slightly higher than those in the “None” group who reported the same, and fewer of the PACE Combo participants than “None” felt their pain is *not* controlled (Figure 21B). Both of these results could be related to the increased activity the "PACE Combo" group experienced,
as by definition they attended the day center for some period of time at least one day per week.

However, when viewing the pain controlled by medications variable alone (Figure 21), there is a clear difference among groups. At Time 2, adults consuming no services (“None”) had the most respondents feeling their medications adequately control their pain, followed by those who consume only in-home services (“Only Others”) and finally the PACE Combo group. This may be because the PACE Combo group was active and engaged and therefore eliciting more pain, increased assessment and therefore attention drawn to pain by PACE staff, or a combination of these two and other factors.

![Figure 20. Medication and Medication-Related Variables by Service Group. A) Medication Variables and B) Medication-related Pain Control.](image)

**Psychosocial variables**

A clear decrease in isolation and loneliness can be seen in the PACE Combo group, as they declined in both isolation and loneliness from Time 1 – Time 2 (Figure 22). The Only Others group also saw a decline, but less than the PACE Combo group,
and those adults receiving No PACE program services actually rose in both loneliness and isolation.

Figure 21. Psychosocial Variables by Service Group. Isolation and Loneliness rose in the "None" and both declined in the "Only Others" and the "PACE Combo" group.
Figure 22. All Variables by Participants who Increased Services.

Figure 23. All Variables by Participants who Decreased Services.
Although the change data was not significant (see Table 15), stability and variability can be seen when changes to PACE services groups are viewed together by increases or decreases in service consumption. In Figure 22, pain variables clearly decreased in those who increased services by 1 and did not change in those who decreased by 2 (Figure 24). Participants who changed to engage in the most services declined in both loneliness and isolation, whereas those who increased by fewer services rose slightly. When viewed together, Figure 23 shows that, overall, increasing services by 2 led to the most desirable results: stable pain intensity and pain frequency scores, improved loneliness and isolation, and the least reduction in pain control. This suggests that adults who made no changes were participating in the right amount of activities, or that they had no significant changes in health status that would make participation in activities stressful rather than enjoyable.

**DISCUSSION**

**Overall PACE performance**

PACE New Orleans is meeting the needs of its participants. Pain is a complex problem with a wide variety of biomedical and psychosocial players, and PACE New Orleans uses a variety of methods to address this complexity. T-tests revealed the differences between Times 1 and 2 were statistically significant in measures of pain intensity and pain frequency with measures declining. Isolation decreased non-significantly from Time 1 – Time 2, and loneliness also declined and was significant. Last, the medication-related variables all decreased from Time 1 – Time 2: number of medications and the type (in order of descending specificity and complexity) decreased; however, so too did patients’ perception that pain medications adequately controlled pain.
The t-tests indicate that PACE participants have access to socialization opportunities but may need more options for pain control. The data reflect that pain medication complexity increased over time. It may be that many OTC medications were discontinued and therefore, when patients experienced transient pain they were without an immediate solution.

Pain is undertreated in minority populations (Green et al.), and has been shown to be both experienced and reported differently in men and women (Paller, Campbell, Edwards, & Dobs). It is therefore important to know the status of an organization’s treatment of its participants. Importantly, these analyses shows that the PACE program equally serves all its participants regardless of age, race or sex, equally: there were no statistically significant interactions between any of the pain metrics and these control variables.

The overall t-tests also revealed that services consumption declined from Time 1 – Time 2. This may be due to patients’ declining health, which limits the day center’s ability to care for medically involved participants, possible changing demographics of the neighborhood, or any number of shifts in patient circumstances (housing, caregiver availability, etc.). Although service consumption decreased, reports of both isolation and loneliness decreased. This suggests that PACE meets the needs of the changing health of its participants by tailoring services to each person: as health status changes, PACE seems to have responded with a shift in the opportunities for social interaction with staff and/or other participants or caregivers, engagement in activity, and/or increased opportunities for exercise and movement. This is likely possible because of the
flexibility imbedded in the PACE program and the ability of participants to attend a day program, enroll in at-home services, or engage in a combination of both.

**Pain Intensity**

Looking at the pain intensity variable specifically, a more complex pattern emerges. A significant difference emerged between the groups who engaged in no activities and the PACE Combo group at Time 2. This indicates that changes occurred due in some part to services rendered between admission (Time 1) and this later time point. Because data were coded to reflect the PACE Combo group as those attending the day program in *some* measure during the week and the mean difference between the None and the Only Others groups was not significant, this suggests the mechanism responsible is some element of the combined activities and services available at the day center. PACE facilities are required to provide programming and staff activity directors or recreation therapists in order to assure the interventions are appropriate and beneficial to their participants. At minimum, certification as Activity Director is required to work as such at all Louisiana nursing homes, and the facility where these data were collected employed a full-time Recreational Therapist who coordinated activities with the nursing and physician staff, therapists and chaplain. This truly reflects the PACE program’s philosophical perspective of providing culturally sensitive care to its elders.

At Time 2 the PACE Combo group retains the largest number of participants reporting they had *no pain*, indicating that regardless of their health upon admission, attending the day center was beneficial in pain control. Furthermore, the PACE Combo group is the only group in which no participants responded pain was “at times excruciating.” The group who consumed only in-home services had fewer responses in
this category than the "None" group i.e., those who engaged no PACE services at all. Together these data indicate that attending the PACE day program in some measure (hours per day or days per week) is associated with better pain control, followed by engaging services in-home. Social engagement, novelty and movement are likely highest for the PACE day program attendees, making a mechanism associated with one of these likely.

**Pain Frequency**

Pain frequency was not statistically different between groups at Time 1, but by Time 2, the difference was statistically significant. At Time 2, the group of participants who were not participating in the day center at all had risen in pain frequency dramatically, while those attending the day center at least some portion of one day per week (PACE Combo) showed a much smaller change in pain frequency. PACE Combo groups are likely exposed to a level of activity that required additional movement/interaction evoking pain. This would explain the increase (+0.2421) in the PACE Combo group and the slight decrease (-0.3889) in the Only Others group, who may have been able to more fully control their level of stimulation.

**Differences in Pain Variable Outcomes**

Pain intensity and frequency are related but distinct indicators of pain experience. That is, pain may be intense but fleeting such as that experienced in a heart attack, or persistent but dull as in a muscle strain. It is therefore valuable to include both measures in this analysis; however, because data were stratified by diagnosis, we cannot be sure if an enriched environment is more beneficial to one diagnosis or another.
Isolation and Loneliness

Isolation was higher in the "None" group than in the PACE Combo group, and this is an important finding. Loneliness is an important topic of discussion as a measure of an individual’s opinion and emotional state, and these are undoubtedly important factors to consider in a holistic treatment plan. Loneliness may be address by one-to-one interventions such as music or art therapy, assignment of volunteer, or engaging participants with particular tasks at the facility.

Psychosocial factors are an important consideration in physical health, pain experience, quality of life, and mental health. For older adults, these data clearly show a great psychosocial advantage to attending the PACE New Orleans day program. However, should this be undesirable or not beneficial, receiving PACE program services in-home is an excellent alternative to address loneliness and isolation in older adults. In this way, the PACE model is true comprehensive care that includes both enriching experiences and medical care for adults in a variety of health states.

Changes in pain variables

The change data (Hypothesis 2: Changes in pain intensity, frequency, and pain control are associated with change in services from Time 1 to Time 2) further explain the relationship between attending the PACE day center and these pain variables. When pain intensity and frequency are analyzed and include changes in services, groups who increased services had lower scores of both indices (0.73446 and 1.09668, respectively). Further, participants who increased services by 1 had a mean change in isolation from Time 1 – Time 2 0.7143 points lower than those who made no changes to their services routines, and those who decreased by fewer services had a higher loneliness score than others by almost one whole point (0.9346). This supports the theory of self-
efficacy as a moderator in the pain experience: groups who increased services saw a reduction in isolation, loneliness scores, pain intensity and pain frequency.

**Change in Isolation and Loneliness**

Isolation has been shown to be an indicator of mortality risk, but loneliness as an indicator of quality of life should not be discounted. PACE New Orleans shows a strength in its ability to meet this need, as groups who increased services had lower loneliness and isolation scores than groups who made no changes or decreased services. The MDS is important because it has both an objective (isolation) and subjective (loneliness) measure of patient social interaction. Rather than using measures independently, the data could be used to screen for risk and adjust biological health outcomes such as blood pressure and nutrition intake appropriately. In those whose loneliness scores are higher without an accompanying high isolation score, the focus may shift to psychosocial variables, making an effort to create opportunities for self-efficacy, building social capital, and other means of care (such as spiritual support) meaningful to individual patients.

**Medication and medication-related variables**

When considering medication changes in this sample, it is helpful to view all medication-associated variables (Number of Medications, Medication Type, and Patient Perception that Medications Adequately Control Pain) together. A t-test showed an overall decrease in both the number and complexity of medications from Time 1 – Time 2 for all PACE program participants. When examined more closely for changes between Times 1 & 2 by service changes, the largest mean difference in medication type was between those who decreased services by 2 and those who increased by 2. Accordingly,
the participant assessment that their pain medications adequately control pain, showed those who made no changes took more medications. This is in alignment with the one-way ANOVA analysis which revealed a significant difference between the None the PACE Combo groups, with the None group reporting a higher mean pain control score by 0.2955 F (2.124) F=2.906, p≤0.78 This implies that medication adjustments may have been too severe or too fast, especially if participants were increasing activity levels.

Decreasing the number of medications by increasing their ability to address multiple of more complicated types of discomfort is a worthwhile goal. However, in this analysis participants’ feelings of adequate pain control via pain medication simultaneously declined. Because the data were coded to reflect higher scores proceeding toward a more involved pharmaceutical approach to pain management (for example, preventive + prescription pain medication vs. OTC medication alone), this suggests there may be a premature or overaggressive shift toward simplification of medication.

This may put patients in the position of needing additional or more medication to control pain. This is an important finding, as the risk of fall-related injury increases with polypharmacy (Hammond & Wilson, 2013). Decreasing the number of medications overall is one way to control the number of times medications must be administered, as is changing the power and/or complexity of medication. These two approaches must be carefully balanced; decreasing medication to manage polypharmacy may not be wise if the resulting fewer medications do not adequately control symptoms.
CONCLUSIONS
Overall, participants who increase PACE services over time benefit in both biomedical (pain intensity, pain frequency) and psychosocial (isolation, loneliness) measures. This is an indicator of While other successful models of comprehensive care exist, this model of care is indicative of an enriched environment that provides culturally sensitive, patient-centered care to clients with a broad variety of physical, emotional, and spiritual needs, representing the three-tiered social, physical, and novel stimulation suggested by animal EE research as most efficacious stimulation.

RECOMMENDATIONS
In 2002 the United States launched a commission to better understand and make recommendations regarding CAM. Embedded in the report was an acknowledgment that until recently, the Commissions’ response to CAM had been to restrict access to it. This position changed, however, as rigorous and well-designed research began to be published that elucidated and investigated mechanisms of CAM. In the final recommendations section of the 2002 report, the Commission suggests number of actions and policies that will move forward the agenda of CAM, including continued federal, state, non- and for-profit support of CAM research.

The literature on CAM in humans is in its infancy, and more studies with rigorous and well-designed methodologies must be conducted and published. Further, structures are in place – and now encouraged in word and deed by the United States government- to support research funding for programs to continue to investigate the complex interactions that make it successful. Facilities that provide CAM should make completing this research and procuring funding a priority. Partnering with local colleges and universities may be a reasonable first step in expanding programming and research capabilities, and
fostering community support to begin this process. Community engagement would also fill a programming gap which many older adult facilities experience—many facilities suffer from repetitive activity scheduling and would benefit from intergenerational volunteers with broader cultural and geographical diversity.

Additionally, facilities such as PACE New Orleans can and should further assist participants by providing education on non-pharmacological pain control methods such as music, prayer, etc., their participants may use at home. Meticulous records and documentation should be maintained to examine the cost-benefit of these programs over time.

Medicaid and Medicare reimbursements allow for participation of a wide variety of elders, regardless of income; however, more education and community outreach is necessary to increase awareness of these benefits in minority populations. The almost non-existent numbers of Hispanic, Asian and other minority PACE New Orleans participants may be a reflection of this lack of outreach. The low representations of other minority ethnic groups may also be a indication of lack of diversity in ethnic programming and staffing. Additional outreach should be conducted in communities to make elders aware of support services that are culturally appropriate and within economic means.
BIBLIOGRAPHY


CHAPTER 5: CONCLUSIONS

As the global population of older adults continues to increase, the need for efficacious and safe pain control grows as well. This project was launched to understand ways in which environment may augment and enhance traditional medication-based treatment of pain. In particular, this research sought to identify similarities between human populations and rodents and draw relationships between environments, pain medication, and their outcomes. This study is important as it continues to

Literature on the impact of environment upon various conditions continues to grow. For example, the benefits of physical exercise have been thoroughly explored and we now understand the mechanisms by which exercise exerts its benefits, the protective effects it confers, the impact it has upon specific structures of the brain, and which populations benefit most from how much exercise, at what intensity, and when (Voss, Vivar, Kramer, & van Praag, 2013). Environmental enrichment (EE) research is in its infancy, yet many of these questions have been addressed and were either partially or fully answered. To complicate matters, EE confers its benefits through biopsychosocial channels. The beneficial mechanism of environmental enrichment has been proposed to be related to neurotransmitters (biological), self-efficacy (psychological), and social capital (social). The amount of EE is most likely dependent upon the individual, with too much change causing distress and stress-induced analgesia; however, a regulated amount of EE seems to protect against stress-induced analgesia and maintain a more stable level of stress hormones. The positive results of EE in rodent models include faster recovery from surgery, decreased pain in both acute and chronic pain paradigms, increased growth
factors (Ickes et al., 2000), stimulation of neurogenesis (Kempermann, Brandon, & Gage, 1998), and decreased stress hormones (Belz, Kennell, Czambel, Rubin, & Rhodes, 2003). Aged rats respond equally well to EE; with environmental enrichment, older rats are protected from age-associated spatial impairment (Lores-Arnaiz et al., 2006) and attentional deficits (Harati et al., 2011). It is also associated with appropriate stress responses (Segovia, Arco, & Mora, 2009).

The present study has shown commonalities between rodents who were housed in either EE or isolated housing (IH) and humans who either attended a day program, received in-home services, or were more isolated (Table 1).

**Table 16. Comparison of Methodology and Response.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rats</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21 months (83% of lifespan*)</td>
<td>Mean age 76.36 (85% of lifespan**)</td>
</tr>
<tr>
<td>Pain</td>
<td>Isolated vs. Environmentally Enriched, researcher assigned</td>
<td>Isolated vs. Environmentally Enriched, patient reported</td>
</tr>
<tr>
<td>Time</td>
<td>30 days</td>
<td>Variable, minimum 30 days</td>
</tr>
<tr>
<td>Test</td>
<td>Tail Flick, withdrawal from heat source</td>
<td>Minimum Data Set, Self-reported pain intensity &amp; frequency</td>
</tr>
<tr>
<td>Analysis</td>
<td>One-way ANOVA</td>
<td>One-way ANOVA</td>
</tr>
<tr>
<td>Result</td>
<td>↑ pain in isolated group</td>
<td>↑ pain in isolated group</td>
</tr>
</tbody>
</table>

*(Thurman, Bucci, Hart, & Turturro, 1994) **(Administration, 2016)

Animal research is currently the best option available for responsible research into, and development of, pharmaceuticals that will eventually be used by humans. Although there are certainly qualitative and quantitative differences between rodents and
humans, researchers take a great deal of time and care to breed and select the “best fit”
model to ensure the most accurate translation to human subjects. Even with such careful
consideration, variability among subjects and between species is inevitable and
confounding, making the translation from one species to another problematic. For
example, the endomorphin analogs (see chapter 1) deliver antinociception when injected
subcutaneously in mice, but not rats. Additionally, the average drug entering clinical
trials has undergone about a decade of preclinical testing, yet has only an 8% chance of
being approved by the Federal Drug Administration (Shanks, Greek, & Greek, 2009)

Furthermore, some compounds are not toxic in rats or other preclinical species but
the toxicity to humans is discovered in later clinical trials or even after the drug has been
approved. EE does not suffer from any of these risks. Overstimulation is the most likely
negative side effect that may occur from EE, and this may be avoided by employing
trained professionals (activities directors, creative arts therapists) watchful for appropriate
levels of stimulation. EE is already incorporated into most older adult facilities.
Tailoring EE to specific cultures and the abilities of specific residents is simply a matter
of administrative attention. That is, as PACE New Orleans offers culturally appropriate
activities, so too do may others: multi-ethnic music groups in areas with a strong cultural
representation, spirituality meetings incorporating native or naturalized religious groups,
art viewing field trips or lecture series, conversational groups discussing current events,
etc.

Additionally, facilities may aid the EE endeavor by collecting, organizing and
analyzing activity data and resident responses to it. This may be quantitative or
qualitative. Quantitative data is already collected via the MDS; resident interviews in
which quotes about specific activities are collected and shared with staff and family would assist in tailoring activities to better serve their residents.

Analyses were limited to ANOVAs in all studies to more easily draw a relationship between rodent and human subjects. While this was a statistical limitation, it did allow for more direct comparison of these models. However, regression may more fully explain the extent to which variables contribute to an overall experience of pain and would also allow for control of variables such as sex, age, and race. This study and the prior rodent literature have demonstrated the efficacy of EE in rodent models and our work has drawn a relationship between outcomes in rodents and outcomes in humans. The period of preclinical work in EE has produced a robust literature demonstrating excellent physiological and psychological return with minimal risk; it is now appropriate to make national EE recommendations for older adults residing in facilities.

**Implications**

It is impossible to design a study that would accomplish identical conditions in both rodent and human studies, yet accurate prediction of drug response in humans depends upon the ability to replicate animal: human conditions as closely as possible. This research used similar methodology and analyses in both rodent and human studies: both models (rodent and human) had enriched and isolated groups, both contained healthier and sicker subjects, both used subjects whose prior history of enrichment was unknown, both used several pain medications, both included adept and poor exercisers, and both used one-way ANOVAs to analyze data. Although the methodology was different (artificially imposed conditions in rats vs. organically established in humans), the similar pattern of results between species is meaningful.
In order to more thoroughly integrate biomedical and psychosocial aspects of pain, this work was interdisciplinary in nature. That is, both physical (tail flick in rats, pain report in humans) and psychosocial (isolation and loneliness variables in humans) aspects of pain were considered as contributing variables. Pain literature now considers the entire pain experience, including both biomedical and psychosocial aspects, making this work a meaningful contribution to the field. This is particularly important when making recommendations or inferences regarding humans, as in reality is it impossible to control all factors that may be responsible for a change in outcome variables.

**Future Directions**

This study established similarities in the pain experience and behavior of rodent models and human subjects. As suggested by the American Federation for Aging Research (see Chapter 2), we began with younger animals, continued in older animals, and finally studied human participants. Although currently the standard of research design, this methodology is not without flaws. That is, if the differences between mice and rats are large enough to warrant studying two different species (i.e., the EM Analog is successful in mice SubQ, but not effective in rats via the same delivery paradigm), the differences between rats and people may be even larger. The current study has found similarities that warrant additional studies to replicate it and perhaps find additional mechanisms and variables that contribute to the pain experience and efficacy of pain mediation.
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