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Resting state connectivity correlates with drug and placebo response in fibromyalgia patients

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ABSTRACT

Fibromyalgia is a chronic pain syndrome characterized by widespread pain, fatigue, and memory and mood disturbances. Despite advances in our understanding of the underlying pathophysiology, treatment is often challenging. New research indicates that changes in functional connectivity between brain regions, as can be measured by magnetic resonance imaging (fcMRI) of the resting state, may underlie the pathogenesis of this and other chronic pain states. As such, this parameter may be able to be used to monitor changes in brain function associated with pharmacological treatment, and might also be able to predict treatment response.

We performed a resting state fcMRI trial using a randomized, placebo-controlled, cross-over design to investigate mechanisms of action of milnacipran (MLN), a selective serotonin and norepinephrine reuptake inhibitor (SNRI), in fibromyalgia patients. Our aim was to identify functional connectivity patterns at baseline that would differentially predict treatment response to MLN as compared to placebo. Since preclinical studies of MLN suggest that this medication works by augmenting antinociceptive processes, we specifically investigated brain regions known to be involved in pain inhibition.

15 fibromyalgia patients completed the study, consisting of 6 weeks of drug and placebo intake (order counterbalanced) with an interspersed 2 week wash out period. As a main finding we report that reductions in clinical pain scores during MLN were associated with decreased functional connectivity between pro-nociceptive regions and antinociceptive pain regions at baseline, specifically between the rostral part of the anterior cingulate cortex (ACC) and the insular cortex (IC), as well as between the periaqueductal gray (PAG) and the IC: patients with lower preexisting functional connectivity had the greatest reduction in clinical pain. This pattern was not observed for the placebo period. However a more robust placebo response was associated with lower baseline functional connectivity between the ACC and the dorsolateral prefrontal cortex. This study indicates that ACC–IC connectivity might play a role in the mechanism of action of MLN, and perhaps more importantly fcMRI might be a useful tool to predict pharmacological treatment response.

1. Introduction

Fibromyalgia is a chronic pain syndrome of unknown origin, estimated to affect 2–5% in all populations studied (Raspe, 1992; Wolfe et al., 1995; Assumpcao et al., 2009; Dhir et al., 2009). Fibromyalgia is characterized by widespread pain, fatigue, poor sleep, and dyscognition (Wolfe et al., 2010) and is often also associated with mood disorders such as depressive episodes and anxiety. Although the underlying pathophysiology is not entirely understood, fibromyalgia has been associated with augmented central nervous system (CNS) processing of nociceptive stimuli using both quantitative sensory testing (QST) and functional neuroimaging. (Gracely et al., 2002; Desmeules et al., 2003; Petzke et al., 2003; Smith et al., 2008). In this context the notion of dysfunctional endogenous pain inhibition has been proposed to play a pivotal role in the genesis of chronic widespread pain. This is supported by studies demonstrating impaired or absent conditioned pain modulation (CPM) in these patients (Lautenbacher and Rollman, 1997; Vierck et al., 2001; Julien et al., 2005; Chalaye et al., 2014).

In recent years, functional (Gracely et al., 2002; Giesecke et al., 2004; Jensen et al., 2012) and structural (Kuchinad et al., 2007;

Abbreviations: 5-HT, serotonin; ACC, anterior cingulate cortex; BPI, brief pain inventory; CNS, central nervous system; DMN, default mode network; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; fcMRI, functional connectivity magnetic resonance imaging; IC, insular cortex; FEW, family wise error; MCC, mid-cingulate cortex; IPL, inferior parietal lobule; MLN, milnacipran; NE, norepinephrine; PAG, periaqueductal gray; PCC, posterior cingulate cortex; QST, quantitative sensory testing; rs-fc, resting state functional connectivity; SNRI, selective serotonin and norepinephrine reuptake inhibitor; SPM, statistical parametric mapping; TMS, transcranial magnetic stimulation.

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Schmidt-Wilcke et al., 2007; Ceko et al., 2013) brain imaging studies have shed some light on possible central mechanisms that might play a role in the genesis of chronic pain in fibromyalgia. One such approach is the investigation of fluctuations in blood oxygenation level dependent (BOLD) signals at rest, termed resting state functional connectivity (rs-fc). This method identifies and assesses the interaction between disparate cortical regions and networks. Only recently have changes in rs-fc been demonstrated in fibromyalgia, such as a hyper-connectivity between the default mode network (DMN), a constellation of brain regions involved in self-referential thought, and the insular cortex (IC), a brain region known to play a pivotal role in pain perception (Napadow et al., 2010). Interestingly this hyper-connectivity may be a marker for chronic pain intensity as two independent trials have shown that decreases in connectivity between the DMN and IC following treatment were associated with reductions in clinical pain (Napadow et al., 2012; Harris et al., 2013).

Treatment of fibromyalgia in terms of a clinically relevant reduction in widespread pain is often challenging and both pharmacological and non-pharmacological approaches (Bernardy et al., 2013). To date, three drugs have been approved by the U.S. Food and Drug Administration for the treatment of pain in fibromyalgia: pregabalin, a compound that binds to the $\alpha_2\delta$ subunit of a voltage dependent presynaptic calcium channel, and two selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors, milnacipran (MLN) and duloxetine (Goldenberg et al., 2010; Schmidt-Wilcke and Clauw, 2010; Schmidt-Wilcke and Clauw, 2011). Other drugs, such as tricyclic compounds (TCA, e.g. amitryptiline), viewed as non-selective 5-HT and NE reuptake inhibitors, have also repeatedly been shown to be efficacious in the treatment of fibromyalgia and are frequently used in pharmacological treatment regimens. The way 5-HT and NE reuptake inhibitors act to reduce pain is still a matter of debate as spinal, subcortical, and cortical mechanisms have all been proposed. However the overall effect of any of these individual treatments has been modest (Häuser et al., 2013). Moreover a key limitation in the treatment of fibromyalgia, and chronic pain in general, is that there are no reliable tools to guide treatment assignment for individual patients. As such, clinical routine largely relies on trial and error.

Recently our group has shown that chemical and functional imaging in fibromyalgia can be used to predict treatment response to pregabalin in fibromyalgia (Harris et al., 2013). Here we sought to identify rs-fc patterns that might predict treatment response in fibromyalgia to the selective 5-HT and NE reuptake inhibitor MLN. Since preclinical studies have indicated that dual reuptake inhibitors are thought to have a favorable effect on endogenous pain inhibition which is believed to be dysfunctional in fibromyalgia (Lautenbacher and Rollman, 1997; Julien et al., 2005), we specifically focused on rs-fc to brain regions involved in antinociception and pain modulation such as: the periaqueductal gray (PAG), the rostral part of the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC) and the amygdala.

2. Material and methods

2.1. Subjects

We investigated 23 female patients diagnosed with fibromyalgia. Inclusion criteria were: (1) meeting 1990 American College of Rheumatology criteria for FM with chronic widespread pain for at least 6 months; (2) 18–70 years of age; (3) non-lactating and non-pregnant; (4) right handed; (5) score between 40 and 90 mm (inclusive) on a 100 mm pain Visual Analogue Scale (VAS); (6) willing to withdraw from CNS-active therapies marketed as antidepressants (monoamine oxidase inhibitors, tricyclics, tetracyclics, selective serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, and SNRIs); (7) willing to withdraw from stimulant medications such as those used to treat attention deficit disorder and attention deficit hyperactivity disorder (e.g. mixed amphetamine salts, methylphenidate, dextroamphetamine) or fatigue associated sleep apnea or shift work (e.g. modafinil); (8) willing to withdraw from anorectic agents such as diethylpropion, sibutramine, and phentermine; and (9) if currently taking pregabalin and/or gabapentin, to remain on a stable dosage throughout the duration of the study. Major exclusion criteria were: (1) significant risk of suicide; (2) medical conditions including cardiac diseases, glaucoma, autoimmune disease, systemic infections (e.g. human immunodeficiency virus, hepatitis), active cancer, pulmonary disease or dysfunction, unstable endocrine disease (must be stable at least 3 months prior to study enrollment), unstable diabetes, unstable thyroid disease; (3) pregnant or lactating; (4) any other severe, acute, or chronic medical or psychiatric conditions that could increase risk or interfere with trial results; (5) body mass index greater than 36; (6) treatment with any experimental agent, including MLN, within 30 days before screening; and (7) contraindications with MRI procedures.

All study participants gave written informed consent. The study protocol and informed consent documents were approved by the University of Michigan Institutional Review Board (Ann Arbor, Michigan) and Forest Laboratories (New York, NY). All clinical data were verified for accuracy and the database was locked before analysis. All imaging data were stored, validated, analyzed, and assessed for quality at the University of Michigan independent of Forest personnel. Patient demographics, medications, and identification of inclusion for analysis are listed in Table 1.

2.2. Treatment

All patients were randomized in a double-blind, two-period crossover study of MLN versus placebo (Fig. 1). Potential participants underwent an initial visit, prior to the first neuroimaging session, wherein they were evaluated for study criteria. After meeting inclusion/exclusion criteria, consenting patients were randomized to either MLN first or placebo first for Period 1, and which followed 1–4 week washout period to withdraw from all excluded medications that could interfere with efficacy and neuroimaging measures. This washout period included a 1-week single-blind placebo run-in period to reduce the possibility of placebo effects during the first double-blind treatment period. Following the placebo run-in period, all participants underwent their first neuroimaging scan (pretreatment for Period 1) which involved functional connectivity magnetic resonance imaging (fcMRI). Following this initial scan, subjects randomized to receive MLN in the first period, underwent dose escalation of MLN up to 200 mg/day over the course of 2 weeks, with a maintained fixed dose for 4 weeks, at which time an identical post-treatment fcMRI session was conducted. Those subjects randomized to placebo for Period 1 took matching placebo pills over the course of 6 weeks before undergoing an identical post-treatment fcMRI session. Results from post-treatment scans will be presented elsewhere. All participants then entered a 1 week taper and 2 weeks of a placebo washout, during which time a placebo sugar pill was consumed daily. Once the washout period was completed, all patients crossed over to the other study drug for Period 2 (i.e. those who had MLN for Period 1 received placebo for Period 2 and vice versa.). Neuroimaging sessions for Period 2 were identical to those in Period 1. Placebo data included in all analyses came from either Period 1 or Period 2 (depending on treatment order), and were included for all subjects regardless of treatment order. All subjects were informed that they would be dosed with MLN or placebo at various times throughout the study, but were not told when they were transferred from one treatment to the other. All investigators and research team members were blinded to study drug and placebo timing.

2.3. Pain assessment and analysis

We assessed treatment response for both clinical pain as well as evoked experimental pain in all participants prior to and following