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Effective connectivity predicts future placebo analgesic response: A dynamic causal modeling study of pain processing in healthy controls

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ABSTRACT

A better understanding of the neural mechanisms underlying pain processing and analgesia may aid in the development and personalization of effective treatments for chronic pain. Clarification of the neural predictors of individual variability in placebo analgesia (PA) could aid in this process. The present study examined whether the strength of effective connectivity (EC) among pain-related brain regions could predict future placebo analgesic response in healthy individuals. In Visit 1, fMRI data were collected from 24 healthy subjects (13 females, mean age = 22.56, SD = 2.94) while experiencing painful thermal stimuli. During Visit 2, subjects were conditioned to expect less pain via a surreptitiously lowered temperature applied at two of the four sites on their feet. They were subsequently scanned again using the Visit 1 (painful) temperature. Subjects used an electronic VAS to rate their pain following each stimulus. Differences in ratings at conditioned and unconditioned sites were used to measure placebo response (PA scores). Dynamic causal modeling was used to estimate the EC among a set of brain regions related to pain processing at Visit 1 (periaqueductal gray, thalamus, rostral anterior cingulate cortex, dorsolateral prefrontal cortex). Individual PA scores from Visit 2 were regressed on salient EC parameter estimates from Visit 1. Results indicate that both greater left hemisphere modulatory DLPFC ➔ PAG connectivity and right hemisphere, endogenous thalamus ➔ DLPFC connectivity were significantly predictive of future placebo response ($R^2 = 0.82$). To our knowledge, this is the first study to identify the value of EC in understanding individual differences in PA, and may suggest the potential modifiability of endogenous pain modulation.

Introduction

Despite the prevalence and multifaceted costs of chronic pain, existing treatments remain relatively poor, displaying only a 30% success rate (Borsook et al., 2011a). There is a need to better understand the neural mechanisms underlying pain processing to formulate more effective treatments and enhance currently existing therapeutic modalities (Borsook et al., 2011b; Tracey and Mantyh, 2007). Specifically, additional clarification of the cortico-cortical interactions involved in placebo analgesia may aid in meeting this need (Wiech et al., 2008). Given the variability observed in placebo response across studies (Price et al., 2006, 2008), neural factors predicting individual differences in placebo analgesic response could likely aid in treatment decision and personalization of treatment to aid in the optimization of pain interventions.

A number of studies have investigated the neural factors involved in differences in individual response to placebo analgesic manipulations (Pecina et al., 2013; Schweinhardt et al., 2009; Scott et al., 2007; Wager, 2005; Wager et al., 2011). In studies by Schweinhardt et al. (2009) and Scott et al. (2007) increased gray matter density and dopamine release, respectively, in reward-processing areas of the brain were associated with greater placebo response. Wager (2005) also found that differences in BOLD activity during anticipation and delivery of painful stimuli in emotion processing regions were predictive of placebo analgesia. Evidence suggests that measures of intra-regional connectivity may be more sensitive to changes in pain experience and modulation (Wartolowska, 2011) than the methods used in the abovementioned studies, potentially limiting their utility.

Some evidence exists to suggest that structural and functional connectivity may aid in predicting placebo response. A diffusion tensor imaging study (DTI) of placebo analgesia (Stein et al., 2012) demonstrated that greater placebo responses were associated with increased white matter integrity and connectivity among regions that contribute to the descending pain modulatory system (DPMS; e.g. DLPFC, rACC, thalamus, and PAG) were associated with greater placebo response. These authors suggested

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that greater white matter integrity might predispose individuals toward more effective top-down modulation of pain. These results affirm the role of direct connections between DPMS regions in predicting individual differences in placebo response. These studies, however, used measures of neural activity concurrent to the placebo response. Additional clinical utility would be offered through the identification of neural mechanisms predictive of individual response to future placebo conditioning. Identification of specific, directed inter-regional couplings involved in placebo analgesia could aid in the identification treatment responders or serve as potential sites for mechanism-based interventions.

Few studies have identified neural mechanisms that are predictive of response to future placebo conditioning. Hashmi et al. (2012) investigated this relationship and indicated that in chronic back pain patients, placebo responders and non-responders exhibit distinct spatial patterns of DLPFC functional connectivity at baseline, two weeks prior to the assessment of placebo response. This lends additional support for the role of functional interactions among DPMS regions in predicting placebo response.

Work by our group has indicated placebo analgesia results in considerable changes in the directed influence among pain-related brain regions or effective connectivity (Craggs et al., 2007). Individual differences in pain-related effective connectivity *before* receipt of placebo may provide additional value in the prediction of placebo response; however, this relationship has not yet been explored. The present study aimed to investigate the role of pain-related effective connectivity in predicting future placebo response. To do so, we estimated the effective connectivity among the set of regions whose connectivity was found to be salient in placebo analgesia (Craggs et al., 2007; Stein et al., 2012): the thalamus, rACC, DLPFC and PAG. By viewing placebo response as a continuous variable and modeling effective rather than functional connectivity, we were able to identify potentially meaningful sources of variability obscured by previous research (Hashmi et al., 2012), which has not yet examined the role of directed neuronal couplings in understanding individual differences in placebo response. We hypothesized that greater descending connectivity estimates from cortical brain regions (rACC, DLPFC) would be associated with greater placebo response during subsequent placebo conditioning.

Methods

These data come from a portion of a larger research investigation of the neural substrates of placebo analgesia. Data included in the present analyses represent brain activity associated with thermal stimuli from the parent study's baseline visit and behavioral ratings associated with thermal stimuli from the study's placebo-conditioning visit. Baseline "pain" and "placebo" temperature thresholds were individually determined using VAS responses to thermal quantitative sensory testing (QST) during an initial screening visit. Methods described below represent procedures used for the baseline and placebo-conditioning visits.

Participants

Data from 24 healthy individuals were analyzed in this study (mean age = 22.59, SD = 3.06, 13 females). Twelve participants were identified as White, seven as Asian, five as Hispanic, four as African American, and one as Native Hawaiian or Pacific Islander (some selected multiple categories). Participants were excluded if they met the following criteria: 1) current enrollment in another research study that could influence participation in the present study, 2) use of pain-related medications that could not be stopped seven days prior to testing (e.g., NSAIDs, antihistamines, antidepressants, anti-convulsants, migraine medications, and cough suppressants), 3) history of psychiatric, psychological, or neurologic disorder, as well as medical conditions associated with chronic pain, 4) current medical condition that could affect study participation, 5) positive pregnancy test result in females, 6) presence of metal within the body, and 7) inability to provide informed consent. The University of Florida Institutional Review Board approved the present study. All participants provided written informed consent.

Experimental materials

Thermal stimuli during fMRI scanning periods were delivered using an MR-compatible, peltier-element-based stimulator (Medoc Thermal Sensory Analyzer, TSA-2001, Ramat Yishai, Israel). Temperatures produced by this device range from 33 °C to 51 °C. Participants reported

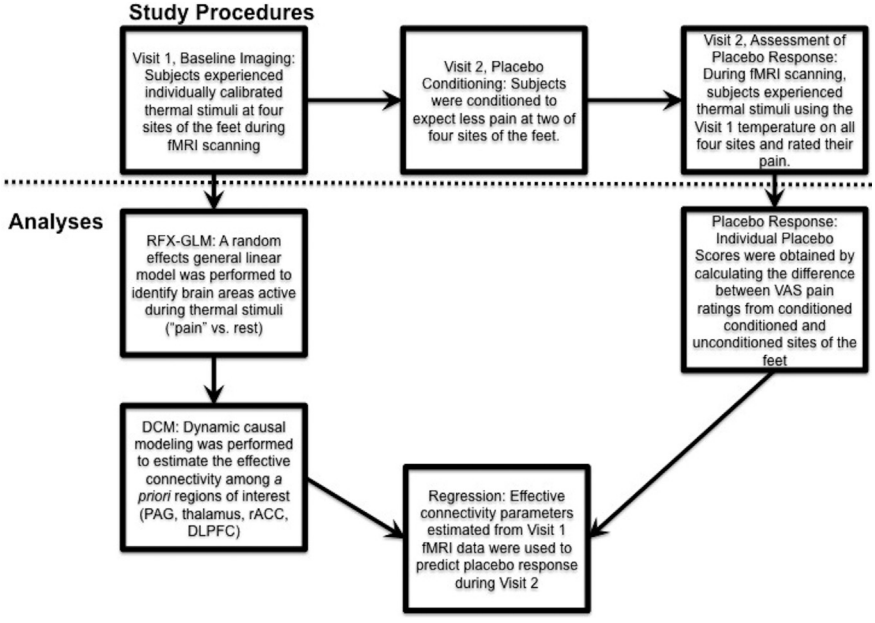

Fig. 1. Experimental procedures and corresponding analyses are shown in the schematic above. Abbreviations: DLPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; PAG, periaqueductal gray.