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Using optimal combined moderators to define heterogeneity in neural responses to randomized conditions: Application to the effect of sleep loss on fear learning

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ABSTRACT

Comparing the neural outcomes of two randomized experimental groups is a primary aim of many functional neuroimaging studies. However, between-group effects can be obscured by heterogeneity in neural responses. Optimal Combined Moderator (OCM) approaches have previously been used to clarify heterogeneity in clinical outcomes following treatment randomization. We show that OCMs can also be used to clarify heterogeneity in the effect of a randomized experimental condition on neural responses. In 78 healthy adults aged 18–30 from the Effects of Dose-Dependent Sleep Disruption on Fear and Reward (SFeRe) study, we used demographic, clinical, genetic, and polysomnographic characteristics to develop OCMs for the effect of a randomized sleep restriction (SR) versus normal sleep (NS) condition on blood-oxygen-level dependent responses in the right amygdala (RAmyg) and subgenual anterior cingulate cortex (sgACC) during fear conditioning (FC) and extinction (FE) paradigms. The OCM for the RAmyg during FE was strongest [r (95% CI) = 0.52 (0.42, 0.68)], withstood cross-validation, and divided the sample into two subgroups with opposing experimental effects. Among N = 48 participants ("SR < NS"), those with SR exhibited less RAmyg activation during FE than those with NS [d (95% CI) = −1.10 (−1.86, −0.77)]. Among the remaining N = 30 participants ("SR > NS"), those with SR exhibited greater RAmyg activation during FE following SR than those with NS [d (95%CI) = 0.87 (0.37,1.78)]. SR > NS participants were more likely to be female, white, l/l genotype carriers, and have a psychiatric history. They had less sleep (overall and in REM), lower REM density, and lower spindle activity (12–16 Hz). Applying OCMs to randomized studies with neural outcomes can clarify neural heterogeneity and jumpstart mechanistic research; with further validation they also offer promise for personalized brain-based treatments and interventions.

1. Introduction

1.1. Heterogeneity in neural responses to randomized experimental conditions

Comparing the neural outcomes of two randomized experimental groups is often a primary aim of functional neuroimaging studies across a wide range of research topics, including depression (Dunlop et al., 2017; Li et al., 2016; Williams et al., 2015), anxiety (Faria et al., 2017; Gingnell et al., 2016), cognition (Suo et al., 2016; Rosen et al., 2011), and sleep (Dalmases et al., 2015; Gorfine et al., 2006), among others [e.g. (Lesage et al., 2017; Sladky et al., 2015; Kumar et al., 2014; Kirk et al., 2014; Shpaner et al., 2014)]. However, within a randomized experimental group, it is common to observe heterogeneity in the level of blood-oxygen level dependent (BOLD) signal change (i.e., relative activation or deactivation) within a region of interest in response to a given

Abbreviations: CS-, Conditioned Safety Cue; CS+, Fear Conditioned Stimuli (CS+1 or CS+2); CS+1, Fear Condition Stimuli #1; CS+2, Fear Condition Stimuli #2; CS + E, Extinguished Fear Conditioned Stimuli; EEG, Electroencephalography; FC, Fear Conditioning; FE, Fear Extinction; NS, Normal Sleep; OCM, Optimal Combined Moderator; PSG, Polysomnography; RAmyg, Right Amygdala; REM, Rapid Eye Movement; SFeRe, Effects of Dose-Dependent Sleep Disruption on Fear and Reward; sgACC, Subgenual Anterior Cingulate Cortex; SR, Sleep Restriction; vmPFC, Ventromedial Prefrontal Cortex.

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stimulus. That is, some individuals display greater (de)activation while others display less (de)activation. This heterogeneity can make it difficult to observe meaningful between-group differences in the full sample. Clarifying heterogeneity by defining subgroups with similar neural responses under one experimental condition versus another can enhance the robustness and clinical implications of findings in the field of neuroimaging, and with additional validation could eventually contribute to personalized brain-based interventions and treatments.

Heterogeneity in neural responses is common in the study of the effects of sleep restriction (SR) as well as in fear learning [e.g. (Van Dongen et al., 2012; Altena et al., 2008; Venkatraman et al., 2011; Drummond et al., 2000, 2013; MacNamara et al., 2015)]. We previously observed heterogeneity in neural responses to SR in our own Effects of Dose-Dependent Sleep Disruption on Fear and Reward (SFeRe) study (Log # 11293006). SFeRe aimed to examine the effects of SR versus normal sleep (NS) on neural indices of emotional memory processing; namely, fear conditioning (FC; learning that a stimulus signals danger or an aversive outcome) and fear extinction (FE; learning that the stimulus is no longer dangerous after repeated presentation without the anticipated aversive outcome). To this end, SFeRe randomized healthy adults to a night of SR or NS and then measured BOLD signal changes in response to conditioned versus safe stimuli (FC) and extinguished versus safe stimuli (FE). Within SR and NS groups, some participants exhibited greater activation in pre-defined regions of interest [right amygdala (RAmyg) and subgenual anterior cingulate cortex (sgACC)] during FC and/or FE, while other participants exhibited less activation. Moreover, the experimental effects of SR versus NS on neural outcomes were relatively weak and exhibited small effect sizes at best.

1.2. Use of optimal combined moderators to clarify neural heterogeneity

One way to clarify neural heterogeneity in response to a randomized experimental condition – and potentially reveal larger, more meaningful between-group effects—is to identify moderators. In the context of a randomized trial such as SFeRe, moderators are pre-randomization characteristics that are independent of the randomized experimental condition (here a sleep condition: SR versus NS) and which indicate a different experimental effect depending on the value of that characteristic (Kraemer, 2013). For example, if sex were identified as a moderator of the effect of the sleep condition on RAmyg activation during FC, one might observe that females randomized to SR tend to display greater activation relative to females randomized to NS, while males randomized to SR tend to display less activation relative to males randomized to NS. Similarly, if age were identified as a moderator, one might observe that younger individuals randomized to SR tend to display greater activation relative to younger individuals randomized to NS, while older individuals randomized to SR tend to display less activation relative to older individuals randomized to NS.

Moderators are traditionally identified using multiple, separate regressions to determine which baseline characteristics interact with the randomized condition. However, this approach is problematic for two reasons in particular (Kraemer, 2013; Wallace et al., 2013). First, individual moderators often have weak effects, and many neuroimaging samples are not large enough to detect such small effects with statistical significance (Poldrack et al., 2017). For this reason, focusing on measures of effect size with confidence intervals is useful, especially for hypothesis-generating research (Wasserstein and Lazar, 2016). Second, even if multiple strong moderators were identified, they could provide contradictory indications. For example, if both age and sex were separately identified as moderators, it is possible that an individual would be predicted to have greater neural activation following SR versus NS based on their sex but less neural activation following SR versus NS based on their age. It would not be clear how to reconcile these contradictory indications to predict whether the individual would have greater or less activation following SR relative to if they had NS (Kraemer, 2013).

To address these challenges, moderator effect sizes and an Optimal Combined Moderator (OCM) approach were recently developed for randomized settings (Kraemer, 2013) and successfully applied to randomized treatment trials with clinical outcomes (Wallace et al., 2013, 2017; Frank et al., 2015; Smagula et al., 2016). The OCM approach uses a regression framework to optimally estimate weights that reflect the extent to which each moderator distinguishes outcome differences between those in one randomized condition (e.g., SR) versus another (e.g., NS) in the context of the other moderators. These weights are then used to combine information from multiple potentially weak and/or contradictory moderators into a single, stronger, combined moderator, denoted M*. If the predicted values for the two randomized conditions cross within the observed range of M*, it can be used to divide a sample into subgroups with opposing between-group experimental effects (e.g., SR versus NS) on neural outcomes. The subgroups can be characterized to describe individuals predicted to have one type of response (e.g., greater neural activation following SR versus NS) versus another (e.g., lower neural activation following SR versus NS). Moreover, with validation, M* can be used as an algorithm to predict whether a new individual will have one type of response versus another using their baseline characteristics. The OCM approach has proven to be a powerful tool in randomized trials with clinical outcomes (Wallace et al., 2013, 2017; Frank et al., 2015; Smagula et al., 2016), offering potential for personalized medicine. However, it has yet to be applied to neural outcomes.

1.3. Neural outcomes and moderators for the SFeRe study

The SFeRe study provides an opportunity to show how the OCM approach could be a powerful tool in randomized studies with neural outcomes. SFeRe randomized healthy adults to either SR or NS and then conducted FC and FE while measuring BOLD signal changes. In animals and humans, neural circuits underlying FC and FE are well defined (Milad et al., 2006a; Milad and Quirk, 2012; Phelps and LeDoux, 2005). We focus specifically on the RAmyg and sgACC as they are central to FC and FE (Helpman et al., 2016; Phelps et al., 2004) (See Fig. 1). Despite a recent meta-analysis in which the amygdala was not robustly identified (Fullana et al., 2016), a large literature has demonstrated the role of the amygdala in FC and related processes (Duvarci and Pare, 2014). The amygdala is important for establishing and maintaining learned emotional associations for FC acquisition, memory storage, behavioral and physiological responses to fear, retrieval of contextual cues, and FE learning (Blair et al., 2003; Davis and Shi, 1999; Maren et al., 2013; Walker and Davis, 1997). We focus on the RAmyg in particular, which has been shown to have greater activation during FC and FE, as well as stronger associations with behavioral measures, as compared to the left amygdala (Phelps et al., 2004; Buchel et al., 1998, 1999; Cheng et al., 2003; LaBar et al., 1998).

While the ventromedial prefrontal cortex (vmPFC) has been shown to

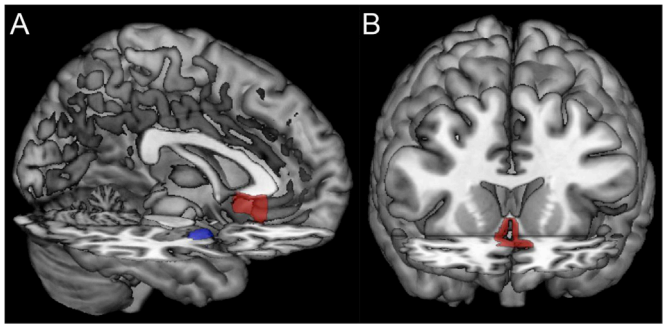

Fig. 1. Region of Interest Masks. Images display (A) a sagittal view of the subgenual anterior cingulate cortex (sgACC, red) and an axial view of the right amygdala (blue), as well as (B) coronal and axial views of the sgACC (red). The sgACC was hand-drawn using MRIcron and the right amygdala mask was defined using the Wake Forest PickAtlas.