

Brain predictors of individual differences in placebo responding

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Abstract

Placebo responses are highly variable across individuals. Explaining this variability is one of the keys to understanding endogenous regulatory processes, and is critical for measuring and controlling placebo effects in all kinds of studies. In this chapter, we review literature on the personality and brain correlates of individual differences in placebo analgesia. An emerging brain literature has used fMRI, opioid binding, dopamine binding, and structural brain imaging to predict the magnitude of individual placebo responses. Brain predictors in prefrontal cortices and ventral striatum/nucleus accumbens are relatively consistent across studies and methodologies, showing promise for understanding the neural bases of placebo analgesia. However, most studies use voxel-wise correlation maps to relate brain measures and placebo analgesia, which do not provide unbiased measures of predictive accuracy. Thus, the utility of these brain measures remains to be determined by larger-scale studies using appropriate analytic methods. Finally, we address an apparent paradox in the placebo literature: Placebo responses appear to be both related to stable person-level variables (e.g., brain structure, genetics, personality) and highly variable across situational contexts. We suggest that a resolution lies in recognizing that placebo responses, like many other psychological phenomena, arise from person $\times$ situation interactions, and that both must be considered jointly in order to understand and predict who will be a placebo “responder” in a given situation.

Keywords

Placebo analgesia; placebo responder; pain; individual differences; brain imaging; situation; personality; multivariate models; machine learning

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Brain predictors of individual differences in placebo responding

One of the most consistent findings in the literature on placebo effects is their inconsistency across individuals. Placebo responses can relieve pain and improve clinical outcomes for some individuals, but others show little or no improvement following placebo treatment. Whereas placebo response magnitude is likely distributed on a continuum across individuals, individuals have often been dichotomized into placebo “responders” and “non-responders.” Assessed in this way, the proportion of “placebo responders” varies dramatically across different paradigms, probably because of variation in the strength and type of manipulation involved. Whereas 30-50% of individuals are typically found to experience positive placebo effects in clinical placebo-controlled trials (Price, Finniss, & Benedetti, 2008), studies that directly manipulate expectations about pain in healthy participants have shown expectancy effects in as much as 90-100% of participants (Atlas, Bolger, Lindquist, & Wager, 2010). In this chapter, we refer to the magnitude of placebo responses on a continuous scale, as there is no conclusive evidence for a bimodal distribution of placebo “responders” and “non-responders.” Whether placebo responses are considered in continuous or binary terms, however, the variability in placebo responses across individuals is real and substantial.

In this chapter, we argue that a placebo response at the level of an individual person is driven by both personal and situational factors. Uncovering the factors that underlie these sources of variation, and how they combine together to create a strong placebo response, is an important goal. It has implications for understanding the nature of placebo effects, for promoting efficiency and reducing bias in placebo-controlled clinical trials, and for the potential application of placebo effects in clinical settings (Shapiro, Struening, & Shapiro, 1979; Wager, Atlas, Leotti, & Rilling, 2011). Predicting and understanding placebo responses on an individual level could have direct implications for participant selection in clinical trials and for ‘personalized

medicine’ – the prescription of treatments based on the individual characteristics of the patient.

Because of its importance in both basic and clinical research, a large number of studies have tried to uncover the role of individual differences and personality factors in the placebo response, with mixed outcomes. In the following sections, we will first describe these previous attempts to characterize individual differences in personality and brain measures predictive of placebo response, as well as their limitations, with a specific focus on methodological challenges in brain imaging studies. We will then discuss the importance of considering the interactions between stable person-level traits and situational context, often referred to as person x situation-interactions (Mischel, 2004; Shapiro et al., 1979), and present possible solutions and avenues for future research on the prediction of placebo responses.

Part 1: Personality and brain predictors of placebo analgesia

a. A mixed history of individual differences in placebo response

A long history of research has attempted to link different personality characteristics with placebo responses (Shapiro & Shapiro, 1997). Interestingly, over the decades there has been a shift in the literature on traits associated with placebo responses. Whereas early studies have often seen the placebo effect as fundamentally pathological—e.g., arising from “hysteria”—and related to traits such as social desirability (Beecher, Mosteller, & Lasagna, 1953; Shapiro et al., 1979), more recent approaches have related placebo responses to more ‘positive’ traits and interpersonal factors, such as optimism.

Although suggestibility is still found to be associated with individual placebo outcome (De Pascalis, Chiaradia, & Carotenuto, 2002; Morton, El-Deredy, Watson, & Jones, 2010), several other personality variables that are negatively related to neuroticism and positively to resilience are showing promise as predictors of placebo responses. For example, trait optimism has repeatedly been shown to correlate with individual differences in placebo responses (Geers, Kosbab, Helfer, Weiland, & Wellman, 2007; Morton, Watson, El-Deredy, &

Jones, 2009; Watson et al., 2009). A recent study found that ego-resilience and agreeableness were positively predictive of placebo analgesia (PA) magnitude, and neuroticism was negatively predictive of PA (Peciña et al., in press). In this vein, putatively ‘dopamine-related’ personality traits such as behavioral activation and novelty seeking are also positively correlated with individual variability in placebo responses (Schweinhardt, Kuchinad, Pukall, & Bushnell, 2008). These findings are consistent with others demonstrating that anxiety has a negative impact on placebo effects (see Table 1)(Lyby, Aslaksen, & Flaten, 2010; Ober et al., 2012).

In addition to stable personality traits, individual differences in emotional and cognitive states—which can vary substantially depending on the context—have important influences on placebo outcomes. Some of the best predictors of placebo analgesia in clinical settings are a trusting relationship with the physician and a positive attitude towards the treatment (Shapiro & Shapiro, 1997). Further, a large number of studies have suggested a crucial role for expectations (i.e. subjectively predicted symptom improvement or pain relief) (Atlas et al., 2010; Atlas et al., 2012; Kirsch, 1985; Morton et al., 2010; Price, Milling, Kirsch, & Duff, 1999; Vase, Robinson, Verne, & Price, 2005) and desire for pain relief (Price et al., 2008). In other settings, when placebo expectations are formed based on the observation of another person experiencing pain relief, PA has been shown to correlate with Individual differences in empathic concern for the observed person (Colloca & Benedetti, 2009).

Although these findings suggest a plausible pattern of traits related to placebo responsiveness, it is important to note that the correlations between trait/state variables and individual differences in placebo analgesia have not been replicated across all studies, and the predictive power of personality measures for placebo response remains relatively low. Arthur Shapiro (Shapiro & Shapiro, 1997), a prominent scholar who did much of this work, summarized those early studies this way: “The number of variables thought to be associated with the placebo effect increased with each study that was reviewed. ...dramatic reports of variables associated with the placebo effect could not be replicated....

Evaluation of these studies clearly indicated to us and others that agreement about what variables were consistently and meaningfully associated with placebo reaction could not be achieved.” This might be in part due to the relatively small sample sizes in some of these studies. Another intrinsic limitation of self-report measures is their subjective nature. Self-reported outcomes, by definition, are limited to processes to which patients have introspective access, and they are colored by incentives, decision biases and heuristics, and cultural display rules (Wager & Fields, in press). In addition, from a conceptual perspective, if placebo responses are driven by situational variables, it is not clear whether personality traits alone should be able to predict a substantial amount of the variance in placebo response magnitude. Previous accounts have highlighted the importance of situational factors and person by situation interactions for placebo effects, as will be discussed in more detail below (Mischel, 2004; Shapiro et al., 1979).

b. Recent advances from brain imaging studies

In the past few years, a growing set of studies focuses on physiological measures, especially neuroimaging-based measures of neurobiological processes, as potential predictors of individual differences in PA. These studies have advanced our understanding of the brain mechanisms underlying placebo effects. Moreover, they can also shed light on the neurophysiological systems that contribute to individual variability in placebo responses.

To date, functional MRI studies of placebo have primarily used pain as the modality of interest. Brain responses to pain are relatively well characterized and involve activation of a widespread set of cortical and subcortical areas, including primary somatosensory areas, insula, cingulate cortex, and thalamus (Apkarian, Bushnell, Treede, & Zubieta, 2005; Bushnell et al., 1999; Iannetti & Mouraux, 2010; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Several studies, described below, have used activity in these characteristic “pain processing” brain regions as an indicator of brain processing of painful events, and tested whether and how they are modulated during placebo analgesia. In addition,

placebo-induced activation outside these regions has been interpreted in terms of supporting context and affective processes that contribute to the creation of PA.

Several fMRI studies converge on the observation that placebo-induced relief of pain is paralleled by *decreased* activation of target regions involved in the processing of nociceptive input (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2011; Atlas et al., 2012; Eippert, Finsterbusch, Bingel, & Buchel, 2009; Meissner et al., 2011; Petrovic, Kalso, Petersson, & Ingvar, 2002; Price, Craggs, Verne, Perlstein, & al., 2007; Wager, Rilling, Smith, & Sokolik..., 2004; Wager & Fields, in press; Zubieta et al., 2005). In addition, PA and expectation of pain relief are also related to *increased activation* in another set of brain regions—thought to underlie endogenous pain regulation along with other processes—including orbitofrontal cortex, dorsolateral prefrontal cortex, perigenual anterior cingulate cortex, and periaqueductal grey (PAG) (Atlas et al., 2012; Meissner et al., 2011; Petrovic et al., 2010; Scott et al., 2007; Wager et al., 2004; Wager & Fields, in press). While direct evidence regarding the specific roles of these prefrontal activations remains scarce, several authors have suggested that they might reflect expectation of pain relief or the maintenance of context representations that are used to create the placebo effect (Krummenacher, Candia, Folkers, Schedlowski, & Schönbachler, 2009; Lui et al., 2010; Petrovic et al., 2010; Wager et al., 2011).

Can we use functional brain imaging data to predict individual differences in PA? Evidence regarding brain correlates related to individual differences in PA comes from a number of studies (summarized in Tables 1 and 2, as well as Figure 1) using different brain imaging techniques and modalities, including functional and structural MRI, PET, and electrophysiology.

In an extensive re-analysis of two previously described experiments (Wager et al., 2011), we used brain activity during expectation and pain experience to predict individual differences in placebo analgesia and placebo-induced decreases in putative ‘pain processing’ brain regions. We used both standard regression analysis, which involves correlating activity voxel-by-voxel

with individual differences in PA, and multivariate LASSO (“least absolute shrinkage and selection operator”, Tibshirani, 1996) regression, which uses brain activation patterns across multiple voxels in order to identify regions that are predictive of placebo response magnitude.

What predicts subjective reports of placebo analgesia: pain-related activity or activity during pain-anticipation? Counter-intuitively, reductions in pain processing brain regions during placebo were not correlated with individual differences in reported analgesia. Rather, brain activity during the anticipation of pain best predicted PA. Specifically, we found that PA was predicted by increased anticipatory activity on- vs. off-placebo in dlPFC, OFC, parietal cortex, and cerebellum, as well as decreased somatosensory activity during pain anticipation (Wager et al., 2011). Intriguingly, a different network, comprising ventral cerebellum, perigenual cingulate, and anterior cingulate cortex, was predictive of individual differences in reduced activation of the pain-processing brain regions (Wager et al., 2011). The only regions found to be predictive of both outcomes—reported PA and reduced activity in pain-processing regions—were pre-SMA and lateral prefrontal cortex. These findings suggest that different outcome measures may reflect different components of the placebo response—and, consequently, different measures may predict reductions in pain and pain-related brain processing. Similarly, another recent study found that subjective pain relief was correlated with increased activation of dlPFC and rostral ACC for a “strong” (expensive) placebo paired with high pain relief during conditioning phase, as well as to decreased activation of dorsal ACC, anterior insula, and thalamus in a “weak” (cheap) placebo condition (lower pain relief during conditioning phase) (Geuter, Eippert, Hindi Attar, & Büchel, 2013). While placebo treatments clearly have antinociceptive effects (Eippert, Bingel, et al., 2009; Wager, Scott, & Zubieta 2007)—even potentially modulating spinal cord signaling (Eippert, Finsterbusch, et al., 2009)—the reduction in nociceptive processing might not be the most important factor driving reductions in self-reported pain in all conditions. In this case, neuroimaging also provides alternative outcomes for identifying placebo responders—e.g., those with reduced activity in pain-

responsive regions—which may ultimately help the field move beyond the exclusive reliance on self-reported outcomes and disentangle the complex influences on self-report.

Prediction of chronic pain and symptom severity in patient populations based on neuroimaging data is important for clinical purposes, but is only beginning to be systematically studied. A recent study investigated how functional connectivity was related to analgesic responses in patients suffering from chronic back pain during a 2-week placebo treatment (Hashmi et al., 2012). Baseline (pre-treatment) functional connectivity in BOLD signal between dorsomedial PFC and bilateral insula cortices was predictive of reduced pain two weeks later, as tested in an independent set of patients. Specifically, patients with persistent pain (i.e., non-responders) showed higher connectivity between dmPFC and insula than those whose pain resolved (responders), and the authors therefore suggested that higher negative affect may prevent placebo-induced pain improvements (Hashmi et al., 2012). In addition, high-frequency activity in the left dlPFC and connectivity of this region to other brain areas including the midcingulate cortex was higher in resolving versus persistent pain. The authors report that together, the two connections (dmPFC-insula and LdlPFC-midcingulate cortex) differentiated resolving from persistent pain with 90% accuracy. This unique attempt to predict pain persistence in patients suggests several promising strategies for future research. For example, as in many clinical studies, it was not possible to ascertain whether the patients with resolving pain improved because of an active placebo process or spontaneous healing and recovery. Studies with a no-treatment arm could help assess how much of the overall improvement is due to the placebo itself.

Resting-state functional connectivity of prefrontal areas might also be predictive for how expectations influence pain in healthy participants. A recent study investigated the relationship between resting-state connectivity and cue-mediated changes in pain experience (Kong et al., 2013). Kong et al. report that increased baseline resting-state connectivity of the right fronto-parietal network with the rostral ACC was positively related to the magnitude of expectancy

effects on pain. Connectivity between the somatosensory network and the cerebellum during rest was also positively associated with reduced pain in the cue-based expectation task. Further, they showed that decreases in pain-processing brain regions and lateral prefrontal cortex during painful stimulation covaried with changes in pain ratings (Kong et al., 2013).

Several studies have also correlated measures of brain *structure* with placebo analgesia. Schweinhardt et al (2009), using voxel-based morphometry, found that grey matter density in nucleus accumbens (NAc), insula, and dlPFC correlated with larger PA. PA was also positively correlated with an average across several putatively “dopamine-related” traits, including novelty seeking and behavioral activation, and these traits were in turn correlated with structural differences in NAc and dlPFC (Schweinhardt et al., 2009). Given these multiple links between personality, brain structure, and placebo outcomes, it would be interesting to investigate in future studies whether specific traits mediate the link between structural characteristics and PA, and how variables from different levels of observation could be integrated in multivariate predictive models.

Additional support for brain structural predisposition for placebo responsiveness comes from a recent diffusion tensor imaging (DTI) study (Stein, Sprenger, Scholz, Wiech, & Bingel, 2012). Stein et al. measured both local white matter anisotropy and structural connectivity—using a tract-finding algorithm—between *a priori* cortical and subcortical regions of interest. Individual placebo analgesia was related to increased “white matter integrity” (higher fractional anisotropy) in the vicinity of rostral ACC and in left dlPFC, as well as to stronger fiber tract connections of these two regions with the periaqueductal grey (PAG) (Stein et al., 2012). These results further highlight the importance of cortical, “top-down” modulatory prefrontal regions, and their connections to the descending pain inhibitory system in the brainstem for endogenous pain regulation.

In contrast to MRI, molecular imaging using positron emission tomography (PET) allows the measurement of the activity of specific neurotransmitters and neuropeptides, and their relationship with PA. A number of pharmacological and brain imaging studies have provided evidence for a role for opioidergic activity in

OFC, dIPFC, PAG, rostral ACC, and other regions in the creation of PA (e.g. Amanzio & Benedetti, 1999; Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Eippert, Bingel, et al., 2009; Levine, Gordon, & Fields, 1978; Scott et al., 2008; Wager et al., 2007; Zubieta et al., 2005). Accordingly, several studies have investigated individual differences in the opioidergic system, suggesting that higher μ -opioid activity (reduced [11-C] carfentanil binding), especially in the area of nucleus accumbens (NAc), predicts stronger placebo responses (Scott et al., 2008). A recent study (Peciña et al., in press) extends these findings by relating opioid activity to personality measures. Peciña et al. reported that different subscales of agreeableness correlated positively and neuroticism correlated negatively with individual differences in both PA and placebo-induced mu-opioid activity in NAc, subgenual and dorsal ACC, OFC, dIPFC, insula, PAG, and thalamus. Opioidergic activity in dorsal ACC and PAG also correlated with reduced plasma cortisol levels during pain (Peciña et al., in press). This study cannot establish a causal relationship between placebo and cortisol; the placebo condition always came second, so overall reductions in the placebo condition could be due to the placebo or natural recovery processes. Nonetheless, the individual differences findings suggest a relationship between the central opioid and neuroendocrine systems.

Another important neurotransmitter associated with PA is dopamine (DA). Scott et al. (2008) showed that, in addition to opioidergic activity, individual differences in DA activity in NAc were correlated with subjective PA. In another study from the same group, individual differences in DA activity in NAc during pain anticipation, as well as NAc activity in an unrelated reward anticipation task, were correlated with PA (Scott, Stohler, Egnatuk, Wang, et al., 2007). Together, these findings further support the idea that the dopaminergic system and reward prediction mechanisms play an important role in PA (see also Schweinhardt et al., 2008).

Whereas imaging studies are powerful in revealing the brain regions associated with pain processing and their modulation by placebo effects, electrophysiology and magnetoencephalography have much higher temporal

resolution, and their usefulness in placebo research has not yet been fully exploited. Several studies measuring event-related potentials (ERPs) elicited by painful laser pulses have shown that placebo leads to reduction in the amplitude of laser evoked potentials, particularly the N2 and/or P2 components (Aslaksen, Bystad, Vambheim, & Flaten, 2011; Colloca et al., 2008; Flaten, Aslaksen, Lyby, & Bjorkedal, 2011; Morton, 2010; Wager, Matre, & Casey, 2006; Watson, El-Deredy, Vogt, & Jones, 2007). These effects indicate a modulation in the neurophysiological processing of painful stimuli as early as ~200 msec after stimulus onset, which correlated with the subjectively experienced analgesic effect (Colloca et al., 2008; Lyby et al., 2010; Morton, 2010). The placebo effects on P2 were reduced for participants with high fear of pain, in line with a reduced analgesic effect for highly anxious individuals (Lyby et al., 2010).

In another recent ERP study, we reasoned that increased prefrontal activations during PA could be functionally related to error monitoring and resolution. During PA, the brain has to adjust to a mismatch (or conflict) between expected and experienced pain, which could be achieved by more general mechanisms involved in conflict and error monitoring (Koban, Brass, Lynn, & Pourtois, 2012). In order to test this hypothesis of a functional relationship between error processing and placebo, we measured ERPs to errors in a go/no-go task during expectation of placebo analgesia. Compared to a matched control condition, placebo analgesia and individual differences in placebo-induced increases in pain tolerance were correlated with an enhanced error-related positivity (Pe) (Koban et al., 2012). This component peaks around 200 ms after error commission and is related to the affective significance of errors and to post-error changes in regulatory control (Ridderinkhof, Ramautar, & Wijnen, 2009; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010). The Pe effect had sources in the lateral PFC and dorsal mediofrontal cortex/SMA, in line with a critical role of these regions in PA (Wager et al., 2011). These results support a functional overlap of prefrontal mechanisms involved in PA and in detecting and adjusting to errors. Our findings are in line with earlier results that have demonstrated additional recruitment of prefrontal areas, especially lateral PFC and OFC, during

placebo compared to opioid analgesia (Petrovic et al., 2010). More studies are needed to investigate which other functional processes might be altered during PA, and how individual differences in cognitive control functions and emotion regulation relate to endogenous pain control.

Taken together, different brain imaging methods and experimental approaches in the last years have started to investigate how placebo effects are influenced by individual differences in brain function and structure. Despite the different methodological approaches and brain imaging techniques, a relatively coherent pattern of brain correlates of PA is emerging (see Figure 1), and some of these effects have been directly linked to personality traits and mental states. Interestingly, only some of these correlations are found in brain areas that are directly involved in the processing of nociceptive input, such as somatosensory areas (S2 and dorsal posterior insula), dorsal ACC, anterior insula, and medial thalamus. Other correlates of individual differences in PA are found in other brain regions, especially in parietal and prefrontal cortex, as well as brainstem areas (see Figure 1).

One consistent finding across several studies is the involvement of neurophysiological systems related to valuation and reward-processing, especially NAc/ ventral striatum, orbitofrontal areas, and vmPFC (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Roy, Shohamy, & Wager, 2012; Schultz, 2004). These activations have been related to individual differences in reward learning (Scott et al., 2007), and to traits including Carver's behavioral activation scale (Carver & White, 1994) and novelty seeking, which may reflect differences in trait dopaminergic activity across participants (Schweinhardt et al., 2009). Individuals with increased functional activity and structural integrity in these valuation regions might be especially prone to placebo analgesia because they efficiently learn to associate medical context and treatment cues with pain relief and reward value. Reward-related activity may also promote opioidergic anti-nociceptive circuits (Leknes & Tracey, 2008), but might also directly alter subjective evaluation and the affective meaning of pain experience (Roy et al., 2012).

Further, as illustrated in Figure 1, one of the most frequently reported correlates of placebo analgesia and relief expectations is the dlPFC (Amanzio et al., 2011; Geuter et al., 2013; Koban et al., 2012; Krummenacher et al., 2009; Meissner et al., 2011; Peciña et al., in press; Petrovic et al., 2010; Stein et al., 2012; Wager et al., 2004; Wager et al., 2011). This region is considered a top-down element of the opioidergic descending pain modulatory system, but also has important roles in cognitive control and conflict resolution (Miller & Cohen, 2001; Nee, Wager, & Jonides, 2007). As such, the dlPFC might maintain context representations and pain relief expectations during PA (Atlas et al., 2010; Wager et al., 2011), which could be crucial to resolve a mismatch between expected pain and actual nociceptive input (Koban et al., 2012; Petrovic et al., 2010). These ideas are also in line with the findings that opioid activity in this region is positively correlated with resilience and negatively with neuroticism (Peciña et al., in press). Future studies might investigate how prefrontal activity and structural properties relate to other important personality predictors of PA related to expectations and emotion regulation, especially optimism (Geers, Helfer, Kosbab, Weiland, & Landry, 2005).

Although this research on brain correlates of placebo effects has increased our insight into the mechanisms underlying PA, much more work is needed in order to find reliable predictors of placebo responsiveness and to tailor clinical placebo treatments to individual predisposition and needs. In the following section, we will highlight some limitations and methodological pitfalls that constrain the current research on brain correlates of individual placebo responses.

Part 2: Limitations of studies on individual differences of PA

Thus far, most experiments on brain predictors of placebo responses have not been specifically designed to study individual differences in placebo responses, and most of their findings, although compelling, await replication. One difficulty in comparing results is the variability in experimental procedures and brain imaging techniques (Figure 1), personality questionnaires, and outcome

measures for placebo effects. Given the cost of brain imaging studies and the need for publishing novel results, replications of previous experiments are often ‘conceptual’ replications rather than exact ones (Makel, Plucker, & Hegarty, 2012; Pashler & Harris, 2012). As a consequence, it is often difficult to determine whether incongruent results are due to differences in experimental design and measures, to lack of statistical power, or to an innate failure to replicate a previous study (Mischel, 1968). This is a very general issue, but one that is amplified for research on brain correlates of individual differences due to the number of tests involved and the diversity of techniques.

A related problem is that not all measures of placebo analgesia are equivalent, as they might be partly driven by different underlying processes. Differences in outcome measures across studies—e.g., reported pain, tolerance, or pain-related brain activity; or pain in different modalities—might explain some of the inconsistencies. Self-reported PA is likely to be particularly complicated and only partly determined by anti-nociceptive processes. For instance, reductions in pain-related processing were unrelated to individual differences in self-reported PA, and were predicted by a different set of brain regions (Wager et al., 2011). In another study, we found no significant correlation between self-reported pain relief and changes in a more implicit measure of PA, pain tolerance temperatures (Koban et al., 2012). Future studies might include a comparison of different PA measures, such as pain thresholds, self-report regarding different aspects (e.g. affect and intensity) of pain and relief, and peripheral and neurophysiological indices of reduced nociceptive processing. An interesting question is whether different outcome measures reflect distinct aspects of PA and could be driven by different processes.

Several other limitations apply to most if not all current studies on brain correlates of individual differences in PA. First, sample sizes in previous studies (typically $N < 30$, always $N < 100$, see Table 1) have been too small to reliably characterize individual differences. In addition, previous fMRI studies have not been designed to accurately measure how well brain activity can predict placebo response magnitude. This is because stringent multiple comparisons corrections

necessary for avoiding false positives means that most true effects will not be detected, and those that are reported suffer from the ‘winner’s curse’—the selection of significant voxels out of a large set of tests can dramatically inflate the apparent effect sizes (Kriegeskorte, Lindquist, Nichols, Poldrack, & Vul, 2010; Lieberman, Berkman, & Wager, 2009; Vul, Harris, Winkielman, & Pashler, 2009; Yarkoni, 2009). Thus, though most brain studies superficially appear to produce strong correlations between PA and brain measures, those effects generally appear much larger than they actually are, and these studies are ultimately inadequate for studying individual differences. If the brain processes that contribute to PA are distributed rather than concentrated in a single anatomical region, the variance explained by any one region is probably small, and can only be detected in much larger samples than currently standard in brain imaging studies (Yarkoni, 2009).

What can be done in order to overcome some of these problems? First, larger sample sizes are needed to investigate individual differences with sufficient statistical power. Second, echoing recent discussions in general psychology, exact replication studies are needed to test and to challenge current hypothesis and functional models (Makel et al., 2012; Pashler & Harris, 2012). And third, the *use of techniques that combine information from multiple brain regions into a single predictive model* can help overcome both the inflation of apparent effect sizes and some of the power limitations of small sample sizes.

This last point deserves further discussion. Studies investigating individual predictors of PA would benefit from the use of procedures explicitly designed to assess predictive accuracy from multivariate data (e.g., multiple brain voxels and/or multi-modal measures) in an unbiased fashion. The use of *holdout sets* for replication and assessment of predictive accuracy have become commonplace in many fields (Hastie, Tibshirani, Friedman, & Franklin, 2005). Cross-validation is a particular method for selecting holdout sets, in which a model is developed on a *training set* of observations and then accuracy is assessed on an independent *test set*. In cross-validation, the model is developed multiple times on different training sets, so that each observation is part of at least one test set. If correctly

applied, cross-validation allows the quantification of how well all the available brain information can predict placebo responses in new patients or participants. Such techniques therefore have a crucial role if we aim at developing tools for predicting outcomes in applied and clinical settings. This procedure represents an important shift away from the use of voxel-wise maps to assess brain correlates of placebo effects, as an *entire brain map* or an *a priori* portion thereof is used to generate an integrated prediction about the outcome (e.g., placebo analgesia), and the predictions are validated on new, independent observations whose ‘ground truth’ need not be known in advance.

Thus far, there have been two studies using such predictive methods to try to predict placebo responders, one predicting placebo responses in healthy individuals (Wager et al., 2011) and the other predicting overall improvement on placebo in chronic low back pain (Hashmi et al., 2012). Both report encouraging results, and this method could be more widely used in the future. However, it is important to note that cross-validation and replication are not panaceas, as they only yield truly unbiased (or minimally biased) measures of prediction accuracy the *first time* the test set is evaluated. If different models are developed after ‘peeking’ at the data in the test sets, the apparent accuracy of the model can be inflated.

In addition to increases in sample size and the use of integrated predictive models, data sharing and pooling across different experiments might also help to identify predictive factors in behavior or brain data (Yarkoni, Poldrack, Van Essen, & Wager, 2010). Indeed, several meta-analyses of placebo effects have begun evaluating the consistency of brain findings (Amanzio, Benedetti, Porro, Palermo, & Cauda, In press; Meissner et al., 2011; Wager & Fields, in press).

The conundrum: Situational variables impact placebo

Even if we follow the recommendations regarding sample size, cross-validation, and other methodological issues, there is one more fundamental limitation in the study of individual differences in PA. It is the power of the

situation, and of interactions between individual predispositions and situational variables.

A necessary prerequisite for the identification of PA predictors based on individual differences is the stability or reliability of placebo responses within individuals across time and situations (Liberman, 1964; Whalley, Hyland, & Kirsch, 2008), but very few studies have investigated re-test reliability and situational stability of individual placebo responses. As long as the experimental setting, placebo treatment, and outcome measures are held constant, individual placebo responses can be relatively stable, as indicated by relatively high test-retest reliabilities between $r = 0.6$ and $r = 0.8$ (Morton et al., 2009; Wager et al., 2004; Whalley et al., 2008), highlighting the stability of individual predispositions *within* situations.

Yet, individual responses can be highly variable when it comes to the comparison of different situations or experiments. An early study (Liberman, 1964) compared placebo analgesia in a group of obstetrical patients across three different situations: Labor pain, post-partum pain, and experimentally induced muscle pain. PA responses were uncorrelated across sessions. Liberman concluded that personality characteristics do not determine individual placebo responses (Liberman, 1964). An important limitation of this study was that the treatment contexts were highly different and the outcome measure of PA very crude, so that the influence of situational factors might have dominated any effect of stable person-level predispositions.

A more recent study investigated more systematically whether placebo responses are reliable across situations (Whalley et al., 2008). Whalley and colleagues measured placebo analgesia across 4 different trials. They used two differentially labeled, but otherwise identical placebo creams (“Ibuprofen” and “Trivaricaine”), which were each tested across two different sessions in the same 71 participants. Whereas they found high correlations across sessions for analgesic responses to the same placebo label (i.e., test-retest reliabilities of $r = 0.60$ and 0.77), the relationship across different labels (brand names) was not significant (Whalley et al., 2008). These results indicate that even minor changes

in placebo treatment have a strong impact on participants' responses, and that individual analgesic outcomes can be very consistent when tested in exactly the same, but not when tested in a different treatment context. The authors conclude that "[...] the search for a generic placebo responder—one who responds consistently to placebo across different situations—can never be successful, and our failure to find general associations between placebo responses and personality measures is therefore unsurprising" (Whalley et al., 2008).

This low consistency of individual responses across different treatment settings illustrates that a very important amount of variance in the placebo response is determined by situational factors—though, as we argue below, it does not mean that stable, person-level variables are not important. Previous research has demonstrated that prior experience, type of placebo treatment, and various other factors related to the psychosocial context or the patient-physician relationship impact the placebo response (Benedetti, 2009; Price et al., 2008; Shapiro & Shapiro, 1997; Wager & Fields, in press). One example is the influence of prior exposure and learning on placebo effects. For example, a greater number of conditioning trials leads to larger placebo effects, makes them more resistant to extinction (Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010), and can even overrule debriefing about the placebo procedure (Schaefer & Wager, 2012). Deception about the treatment might not even be necessary to elicit a placebo response (Kaptchuk, Friedlander, Kelley, & Sanchez..., 2010). On the other hand, it has been shown that suggestion alone can be sufficient to produce placebo effects, albeit weaker than those following conditioning (Amanzio & Benedetti, 1999). Together, these findings suggest that there may be multiple routes to placebo analgesia. If we consider these important situational factors, it might come as no surprise that individuals who show strong PA in one situation might experience little relief in another (Colloca, this book).

Part 3: Solutions

To summarize our discussion so far, the review of the previous literature indicates that personality measures and neurophysiological variables—some of

them likely to be stable person-level characteristics, such as measures of brain structure— have some predictive value for individual placebo responses. At the same time, it is becoming increasingly clear that these predictors are not necessarily always replicable or equally important across different experimental procedures or placebo treatments. Situational factors have a powerful role in determining individual placebo responses. How can we reconcile these opposing perspectives and move toward more accurate predictions of individual differences in placebo responses?

We suggest that this is not a new problem, but one of long-standing controversy in social and personality psychology (often referred to as “person versus situation debate”, e.g. Epstein & O'Brien, 1985; Kenrick & Funder, 1988; Mischel, 1968; Mischel, 2004) concerning whether more variance in behavior is explained by situational factors or by stable personality traits. As in other debates, the truth lies probably in between—or, more precisely, in interactions, as neither person-level nor situational variables alone are sufficient—and a more fruitful approach lies in the integration of the two opposing views. Mischel (2004) proposed that finding stable personality factors requires taking into account situational variability, and especially person-situation-interactions. The temporal stability of personality might even be characterized by how an individual behaves across different situations, which could constitute a relatively stable, person-specific behavioral pattern (Mischel, 2004). For instance, one person could be very outgoing and extraverted when interacting in a small group or with friends, but still be shy in larger group settings and with strangers, whereas another person might enjoy public speaking but be more introverted in smaller groups. Whereas both persons might score intermediate on extraversion when aggregating across situations, their specific personalities would be more finely reflected in the *pattern* of situation-specific individual responses.

From this perspective, placebo effects may be best characterized as driven by complex interactions between individual predispositions such as personality or brain characteristics and situational, contextual factors (Geers et al., 2005; Gelfand, Gelfand, & Rardin, 1965; Mischel, 2004; Shapiro et al., 1979).

In other words, PA requires the right type of person in the right situation, as illustrated in Fig. 2. For example, having an optimistic personality is not sufficient for pain relief (Figure 2, P), nor is a positive suggestion alone (Figure 2, S). However, when an optimistic person receives a positive suggestion, he or she may experience a strong analgesic effect (Figure 2, PxS, see also Geers et al., 2007). The opposite effect might be observed for a pessimistic personality when encountering a negative suggestion. In this case, even an increase of pain (or a nocebo response) may occur (Geers et al., 2005).

This account is in line with the richness of placebo manipulations and the complexity of the mechanisms underlying these effects (Benedetti, 2007; Benedetti, Mayberg, Wager, Stohler, & al., 2005). Whereas one person might respond effectively to a conditioning procedure, another individual may be more susceptible to instructions and conscious expectations of analgesic effects. A third person might be very sensitive to social factors, and therefore respond positively after observing pain relief in another individual (Colloca & Benedetti, 2009) or when the treatment is administered by a trusted care provider. Further, individual prior experience with specific treatments might enhance or counteract positive placebo effects by shaping situation-specific expectations of pain relief or increase. For instance, one of the first participants in our early studies (Wager et al., 2004) dropped out when he learnt that an analgesic cream would be applied to his arm. He told us that he reacts badly to creams, and was sure he was going to get a rash. Unlike for many other participants, the placebo cream was highly aversive, making it unlikely that he would show a placebo response even if he has the right personality, genetics, brain structure, etc. A placebo pill or injection, on the other hand, might have yielded a very different treatment response. Therefore, an important challenge for future research lies in disentangling the different pathways (e.g. conditioned analgesia versus expectations versus social effects) leading to PA and other kinds of placebo effects, and to refine predictions of placebo responses by taking person x situation interactions into account (see Figure 2).

How can brain imaging studies find brain predictors of PA?

Recommendations and conclusions

Despite the inconsistency of placebo responses across different situations, brain predictors can have significant advantage over personality traits such as optimism, agreeableness, or resilience alone. Thus, predictive models using machine learning based on brain activity or functional connectivity might successfully predict PA in new data sets (Hashmi et al., 2012; Wager et al., 2011). Furthermore, fMRI measures such as dlPFC activity (Wager et al., 2011) may increase only when the right person is in the right situation, and thus track the product of person x situation interactions that arise through various means. Functional brain measures might therefore be more powerful in explaining interindividual variance than situational or self-report questionnaire measures alone. Brain measures of anatomy, such as grey matter density or fiber tract connectivity, on the other hand reflect relatively stable factors, and might therefore be predictive only when the situation (and participants' perception of it) is held constant. A promising avenue for future research lies in the investigation of how structural brain anatomy and personality factors relate to each other, and how structural factors and functional brain activity interact during PA.

In order to increase our understanding of individual differences in placebo mechanisms and to be able to better predict the magnitude of the analgesic response for individual participants and patients, several approaches might be productively taken. First, in order to detect stable, person-level predictors of PA, individuals' perceptions of the treatment context (the situational factors) must be as identical as possible. Though it may not be possible to completely control situational variables, it is also possible to measure participants' situation-specific feelings, expectations, and attributions and use them to explain variability in PA. Second, it would be productive to jointly manipulate situational and person-level variables, and to study situation by person interactions (Geers et al., 2005; Geers et al., 2007; Lyby et al., 2010) and how they relate to the level of individual brain responses and neuroanatomical characteristics. Finally, larger scale studies will be needed to provide more conclusive evidence regarding the predictability of

individual differences in placebo responses. Such responses could include multiple types of outcome variables and multiple types of predictors—e.g., personality questionnaires, multi-modal brain imaging, and genotyping—in order to obtain a comprehensive picture of how people and situations interact to produce placebo effects.

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Table 1: Overview over recent studies reporting brain correlates of individual differences in PA. N = number of participants.

<i>Study</i>	<i>N</i>	<i>Personality</i>	<i>Brain Measure</i>	<i>Brain Correlates</i>	<i>Pain</i>
Eippert et al., 2008	48	-	fMRI	rACC-PAG coupling	heat
Elsenbruch et al., 2012	36	-	fMRI	DLPFC, SII, vPCC, Thal	rectal
Geuter et al., 2013	40	-	fMRI	DLPFC, SII, Thal, aIns, dACC, sgACC	heat
Hashmi et al., 2012	30	-	FC-fMRI	VMPFC-Ins	back pain
Koban et al., 2012	20	-	ERP	LPFC, SMA	heat
Kong et al., 2006	16	-	fMRI	DLPFC, IFG, ACC, cerebellum, fusiform gyrus, parahippocampal	heat
Kong et al., 2009	24	-	fMRI	RSFG, RIFG	heat
Kong et al., 2013	46	-	FC-fMRI, fMRI	Insula, precentral, DLPFC, fronto-parietal network-rACC connectivity	heat
Kotsis et al., 2012	36	-	fMRI	Rplns, RPCC, RACC, LsFG, LThal LSTG, RMTG, LMTG, LSMA, RPut, RCer, RCaud, LIFG/Lains	rectal
Lieberman et al., 2004	15	-	PET	RvIPFC, dACC	rectal (IBS)
Lui et al., 2010	31	-	fMRI	RMFG, RIFG	laser
Lyby et al., 2011	33	Stress, Fear of Pain	ERP	N2, P2	heat
Peciña et al., 2012	50	Ego-Resiliency, Agreeableness, Neuroticism, Altruism, Straightforwardness, Angry Hostility	PET (Opioid)	dACC, PAG	saline
Schweinhardt et al., 2008	22	BAS, TCI	sMRI (VBM)	Ins/TC, vStr, MFG, plns	saline
Scott et al., 2007	14, 30	MID task	fMRI, PET (DA, Opioid)	NAC	saline
Scott et al., 2008	20	-	PET (Opioid, DA)	Opioid: sgACC, rACC, oFC, aIns, plns, NAC,	saline

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				rAmy, PAG, DA: NAC, vPut, RvCaud	
Stein et al., 2012	24	-	White Matter DTI	rACC, RDLPFC	heat
Wager et al., 2004	24, 23	-	fMRI	DLPFC, OFC	shock, heat
Wager et al., 2011	47	-	fMRI	Antic OFC, DLPFC, Pre-SMA, reduced S2 area	shock, heat
Watson et al., 2009	11	-	fMRI	aMCC, PCC, postcentral gyrus	laser
Wiech et al., 2010	16		FC-fMRI	aIns-LMCC, aIns-MCC	laser
Zubieta et al., 2006	19	-	PET	DLPFC, rACC, Ins, NAC	saline

Table 2: Legend for studies and contrasts depicted in Figure 1.

Number	Study	Contrast	Modality
1	Wager et al., 2004, Study 1	(Control - Placebo) during pain correlated with Placebo Analgesia	fMRI
2	Wager et al., 2004, Study 1	(Placebo - Control) during anticipation correlated with Placebo Analgesia	fMRI
3	Wager et al., 2004, Study 2	(Control - Placebo) during early pain correlated with Placebo Analgesia	fMRI
4	Wager et al., 2004, Study 2	(Control - Placebo) during late pain correlated with Placebo Analgesia	fMRI
5	Lieberman et al., 2004	(Before - After) placebo treatment correlated with symptom improvement	PET
6	Kong et al., 2006	(After - Before) placebo - (Placebo - Control site) correlated with Placebo Analgesia	fMRI
7	Watson et al., 2009	(Control - Placebo) correlated with Placebo Analgesia	fMRI
8	Wager et al., 2011	(Placebo - Control) during anticipation correlated with Placebo Analgesia	fMRI
9	Wager et al., 2011	(Control - Placebo) during anticipation correlated with Placebo Analgesia	fMRI
10	Wager et al., 2011	(Control - Placebo) during pain correlated with Placebo Analgesia	fMRI
11	Eippert et al., 2009a	(Placebo - Control) - (Saline - Naloxone) correlated with Placebo Analgesia; brainstem	fMRI
12	Stein et al., 2012	FA correlated with Placebo Analgesia	DTI
13	Hashmi et al., 2012	(Decreasing back pain - Persisting back pain) functional connectivity with LdlPFC at baseline	FC-fMRI
14	Hashmi et al., 2012	(Persisting back pain - Decreasing back pain) functional connectivity with LdlPFC at baseline	FC-fMRI
15	Hashmi et al., 2012	(Decreasing back pain - Persisting back pain) HF power at baseline	fMRI (oscillation)
16	Hashmi et al., 2012	(Persisting back pain - Decreasing back pain) LF power at baseline	fMRI (oscillation)
17	Schweinhart et al., 2008	GM density correlated with Placebo Analgesia	VBM
18	Zubieta et al., 2006	Opioid increase correlated with experienced/expected analgesia ratio	PET opioid
19	Elsenbruch et al., 2012	(Control - Placebo) during anticipation correlated with Placebo Analgesia	fMRI
20	Elsenbruch et al., 2012	(Control - Placebo) during pain correlated with Placebo Analgesia	fMRI
21	Elsenbruch et al., 2012	(Responders(Control - Placebo) - Nonresponders(Control - Placebo)) during anticipation	fMRI
22	Elsenbruch et al., 2012	(Responders(Control - Placebo) - Nonresponders(Control - Placebo)) during pain	fMRI

23	Kotsis et al., 2012	(Nonresponders > Responders) during anticipation	fMRI
24	Kotsis et al., 2012	(Nonresponders > Responders) during pain	fMRI
25	Wiech et al., 2010	(Pain Threshold for (High - Low) Threat Stimuli) correlated with functional connectivity with alns during anticipation	FC-fMRI
26	Wiech et al., 2010	(Pain Threshold for (High - Low) Threat Stimuli) correlated with functional connectivity with alns during stimulation	FC-fMRI
27	Geuter et al., 2013	(Strong Placebo - Control) during early pain correlated with PA	fMRI
28	Geuter et al., 2013	(Control - Weak Placebo) during early pain correlated with PA	fMRI
29	Geuter et al., 2013	(Strong Placebo - Control) during late pain correlated with PA	fMRI
30	Geuter et al., 2013	(Control - Weak Placebo) during late pain correlated with PA	fMRI
31	Lui et al., 2010	(Placebo - Control) during anticipation correlated with PA	fMRI
32	Kong et al., 2013	(Good Responders (Control - Placebo) - Poor Responders (Control - Placebo)) during pain	fMRI
33	Kong et al., 2013	(Placebo - Control) correlates with PA	fMRI
34	Kong et al., 2013	Functional connectivity with sensory-motor network correlated with PA	fMRI
35	Kong et al., 2013	Functional connectivity with right frontoparietal network correlated with PA	fMRI
36	Atlas et al., 2010	Brain activity mediators (positive) of cue effects on pain Increases during pain	fMRI
37	Atlas et al., 2010	Brain activity mediators (negative) of cue effects on pain Decreases during pain	fMRI

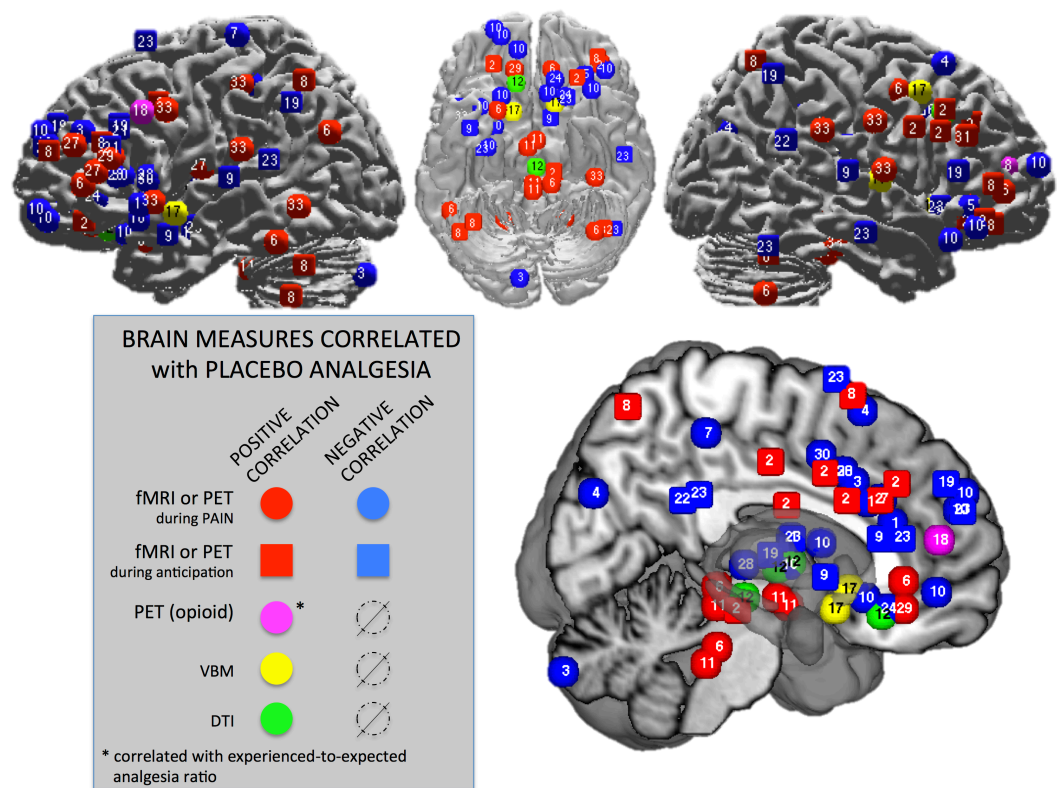
Figure Captions

Figure 1. Brain correlates of individual placebo responses. A) Coordinates from different studies and contrasts, listed by number in Table 2, at which brain measures are reported to correlate with individual differences in PA or to differ between groups of placebo responders and non-responders. Positive and negative correlations from fMRI and PET studies are shown in red and blue, respectively, with spheres and cubes for those points with correlating activity during pain and anticipation, respectively. Magenta spheres denote coordinates at which PET studies found increased opioid activity correlated with the ratio of experienced analgesia to expected analgesia. And locations of gray matter density (VBM) and white matter integrity (DTI) correlates (all positive) with placebo analgesia are marked with yellow and green spheres, respectively. B) Coordinates at which oscillatory measures and functional connectivity findings from fMRI studies are reported to correlate with placebo analgesia (individual studies and contrasts are listed, by number, in Table 2). Included are high frequency band BOLD oscillations (HF) that were positively correlated with placebo analgesia (red), low frequency band BOLD oscillations (LF) that were negatively correlated with placebo analgesia (blue), locations where functional connectivity with left dorsolateral prefrontal cortex (LDLPFC) was positively (magenta) or negatively (cyan) correlated with placebo analgesia, locations where functional connectivity with anterior insula (aIns) during pain (green spheres) or anticipation (green cubes) was negatively correlated with placebo analgesia, locations where functional connectivity with the sensory-motor network was correlated positively with placebo analgesia (orange), and locations where functional connectivity with the right frontoparietal network was correlated positively with placebo analgesia (yellow).

Figure 2. Illustration of possible roles of person characteristics and situation characteristics with respect to placebo response. Each panel diagrams, from left to right, a set of individuals with varying trait

optimism/pessimism levels (an example of a person-level variable) experiencing a positive, negative, or neutral suggestion about treatment efficacy (a situational variable), and subsequently rating the intensity of a painful stimulus. In the 3 panels, the set of outcomes are determined by: (P) only the person-level variable; (S) only the situational variable; and (PxS) an interaction between the two variables. In the interaction case, analgesia is shown by the right kind of person in the right situation, and simple effects of each variable need neither exist nor be easily detectable if they do exist.

Figure 1
A



B

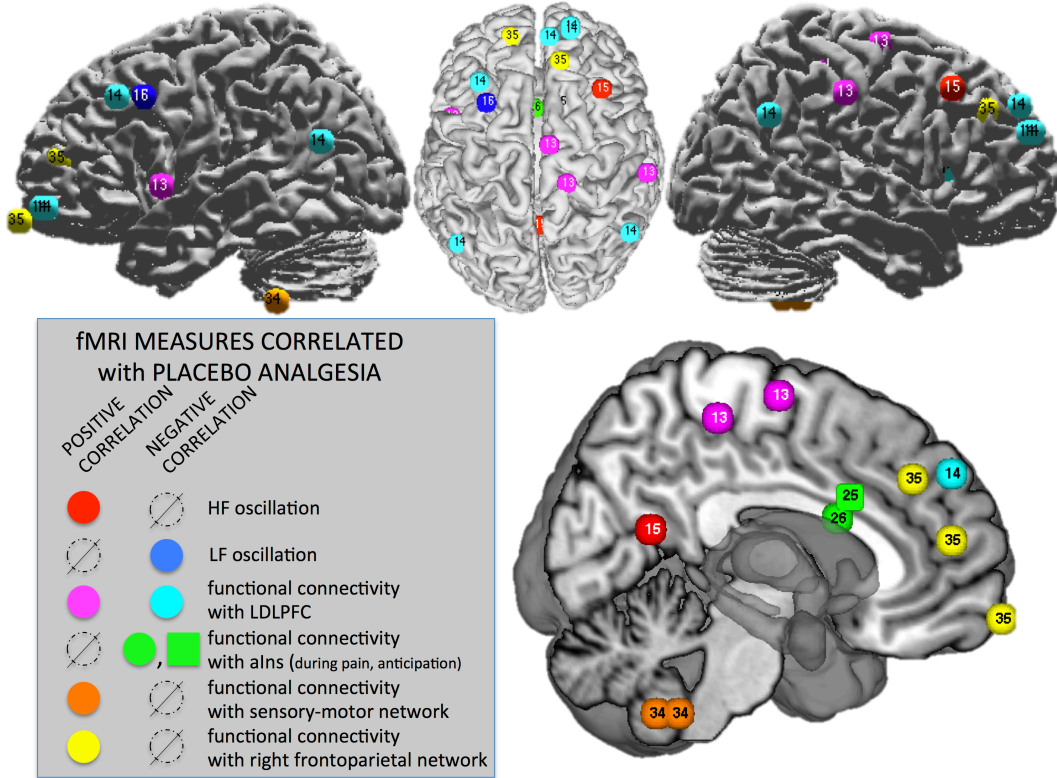


Figure 2

