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REVIEW

Mechanisms of the placebo effect in pain and psychiatric disorders

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Placebo effect research over the past 15 years has improved our understanding of how placebo treatments reduce patient symptoms. The expectation of symptom improvement is the primary factor underlying the placebo effect. Such expectations are shaped by past experiences, contextual cues and biological traits, which ultimately modulate one's degree of response to a placebo. The body of evidence that describes the physiology of the placebo effect has been derived from mechanistic studies primarily restricted to the setting of pain. Imaging findings support the role of endogenous opioid and dopaminergic networks in placebo analgesia in both healthy patients as well as patients with painful medical conditions. In patients with psychiatric illnesses such as anxiety disorders or depression, a vast overlap in neurological changes is observed in drug responders and placebo responders supporting the role of serotonergic networks in placebo response. Molecular techniques have been relatively underutilized in understanding the placebo effect until recently. We present an overview of the placebo responder phenotypes and genetic markers that have been associated with the placebo effect in pain, schizophrenia, anxiety disorders and depression.

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INTRODUCTION

A tremendous amount of research has moved us closer to an understanding of how placebo treatments can alleviate patient symptoms in ways almost indistinguishable from pharmacotherapy. The earliest reports of placebo usage in the scientific literature were mainly in the setting of painful medical conditions[1] and date back at least to the 19th century.[2] A seminal review by Beecher describes placebo treatments that reduced post-operative wound pain in 21–39% of individuals.[3] In the past decade, numerous studies have reported placebo response rates in excess of 40% and this trend of increasing placebo response has been felt most prominently by pharmaceutical companies.[4] Success in clinical trials has decreased significantly in the past decade due to an inability to demonstrate therapeutic efficacy over a placebo control arm. For example, in schizophrenia, the placebo response rate has been reported as the most influential predictor of trial success,[5] contributing to the recent 15% increase in phase 2 trial failures.[6] These reports have piqued the interest of many to investigate the underpinnings of the placebo effect using conventional technologies, such as electroencephalogram, positron emission tomography (PET), functional magnetic resonance imaging and most recently, DNA microarrays.

The incorporation of medical imaging into studies of the placebo effect has considerably expanded our understanding of its neural mechanisms.[7,8] Although molecular techniques have infiltrated most areas of biomedical research, they are markedly lacking in the study of the placebo effect. A small number of investigations in search of serum biomarkers and metabolites provide a different perspective of the placebo effect; however, their results remain challenging to incorporate into current models.[9,10] Unsurprisingly, the genetic underpinnings of the placebo effect are poorly characterized as demonstrated by the lack of a study of familial inheritance. With genotyping assays and whole gene sequencing increasingly being incorporated into the standard of care, pharmacogenomics is altering the approach to prescribing medications.[11] In this review, we will describe the characteristics of the placebo responder phenotype and current hypotheses of placebo mechanisms with emphasis on recent genetic studies in pain, schizophrenia, anxiety and depression.

THE PLACEBO EFFECT AND PAIN

Placebo responder phenotype characteristics

Attempts to characterize the associated phenotypic traits of responders to placebo analgesia have been largely unsuccessful. A summary of sociodemographic and disease trait variables that are predictive of placebo response in painful medical conditions is provided in Table 1. The only trait found consistently among placebo responders is a high baseline pain severity.[12–14] Pain characteristics (for example, acute vs chronic) have not been found to affect placebo response.[15] Only a few studies have reported variations in placebo response based on the age of patients[16,17] or level of education;[17] however, a comparable number of studies find no such associations.[13,14]

Beyond sociodemographics, certain behavioral and personality traits have been associated with responders to placebo analgesia (see summary in Table 2). In an early study, placebo responders were more likely to be 'talkers', regular churchgoers, anxious, self-centered and describe their hospital care as 'wonderful', while non-responders were more 'emotionally controlled', 'withdrawn' and 'less comforted by the care received'.[17] Consistent with placebo responders being described as 'talkers', extroversion has been a reported characteristic of placebo responders in the setting of irritable bowel syndrome (IBS)[18] and experimentally

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Table 1. Predictive variables of placebo phenotype in painful medical conditions

Characteristic	*Condition*	*References*
Age (older)	Wound pain	Lasagna *et al.*[17]
Age (younger)	Migraine	Loder *et al.*[16]
Education (fewer years)	Wound pain	Lasagna *et al.*[17]
Baseline severity (higher)	Neuropathic pain (general)	Irizarry *et al.*[13]
	Osteoarthritis	Zhang *et al.*[12]
	Fibromyalgia syndrome	Häuser *et al.*[14]
	Painful diabetic peripheral neuropathy	Häuser *et al.*[14]

induced pain.[19] Thus far, dispositional optimism has received the greatest support for having a role in the placebo effect. Investigators maintain personality as a moderating variable rather than a predictor variable of placebo effects.[19–21] Dispositional optimism alone is not predictive of placebo response but has been shown to have a statistically significant interaction with situational cues that vary patient expectancy.[20,21] It was also found to be the most significant predictor of placebo response reproducibility.[19]

Guided by findings of dopamine involvement in placebo analgesia, researchers have found novelty seeking, behavioral drive and fun seeking to be correlated with placebo responders in experimentally induced pain.[22] In the same study, gray matter density in the right ventral striatum, a region-of-interest in functional neuroimaging studies, was also found to correlate with dopamine-related personality traits as well as to the placebo effect. A recent PET imaging study of μ-opioid activity during placebo administration in subjects who also underwent a battery of personality tests found placebo responders to have higher scores in neuroticism, extroversion, openness (NEO) altruism, NEO straightforwardness and ego-resiliency while having decreased scores in NEO angry hostility.[23] These four personality traits accounted for 25% of the variance in the placebo response and 27% of μ-opioid activity in the nucleus accumbens (NAC), a key structure in reward processing. This is the first evidence linking personality traits with physiological activity in placebo responders, supporting the hypothesis that personality has a role in placebo response. Given the numerous links made between genetic polymorphisms and personality traits, future studies in this area would be strengthened through the incorporation of genetic testing.[24]

Key studies examining the stability of the phenotype call into question whether situation-independent traits can be reliably associated with placebo responders. Studies with repeated placebo administration find evidence to both support and refute the reliability and consistency of placebo responders.[25] Experiments in placebo analgesia have found that an individual can switch from being a responder to non-responder simply by changing the labeling on the placebo's container, while still verbally suggesting it to be effective.[26] Individuals who responded to one set of environmental cues had a high likelihood of responding again in the exact same environment suggesting that the placebo response is reliable.[19] Given the widely held belief of the placebo effect as a spurious phenomenon, efforts should be made to expand this area of placebo research to better characterize the predictability of placebo responses.

Mechanisms and genetics of placebo analgesia

The neurobiology of the placebo effect has been best characterized in placebo analgesia studies. The first biochemical evidence of the placebo effect demonstrated a role for μ-opioid receptors in non-conditioned[27] as well as conditioned placebo analgesia

Table 2. Summary of personality traits predictive of placebo responders in studies of experimentally induced pain as well as painful medical conditions

Characteristic	*Condition*	*References*
High NEO altruism	Experimental pain[a]	Peciña *et al.*[23]
High NEO straight-forwardness	Experimental pain[a]	Peciña *et al.*[23]
Low NEO angry hostility	Experimental pain[a]	Peciña *et al.*[23]
High ego-resiliency	Experimental pain[a]	Peciña *et al.*[23]
Religiosity	Wound pain	Lasagna *et al.*[17]
Novelty seeking	Experimental pain[a]	Schweinhardt *et al.*[22]
Behavioral drive	Experimental pain[a]	Schweinhardt *et al.*[22]
Fun seeking	Experimental pain[a]	Schweinhardt *et al.*[22]
Openness	IBS	Kelley *et al.*[18]
Extraversion	Wound pain	Lasagna *et al.*[17]
	Experimental pain[b]	Morton *et al.*[19]
	IBS	Kelley *et al.*[18]
Dispositional optimism	Wound pain	Lasagna *et al.*[17]
	Experimental pain[b]	Morton *et al.*[19]
	Experimental pain[c]	Geers *et al.*[21]

Abbreviations: IBS, irritable bowel syndrome; NEO, neuroticism, extroversion, openness. [a]Hypertonic saline masseter pain. [b]Laser-evoked cutaneous pain. [c]Cold pressor pain.

responses.[28,29] Further investigation of the conditioned response suggests that the conditioning method determines if the opioidergic system mediates the analgesic effects.[29,30] The physiology of the placebo effect is also supported by functional neuroimaging studies that demonstrate a correlation between a blood-oxygen level dependent signal in pain-responsive brain regions and the magnitude of placebo analgesia. The regions with the strongest correlations include the rostral anterior cingulate cortex, contralateral insula, 1° somatosensory cortex (S1) and thalamus.[31,32] Coinciding with decreased activation of pain-responsive regions, a large number of studies have found evidence that supports the recruitment of the descending pain modulatory system to provide placebo analgesia.[31,33–38] Imaging studies that have probed neural activity during the anticipation of pain have uncovered the prominent role of the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC). A heightened blood-oxygen level-dependent signal in these regions correlates with subsequent signal depression in pain responsive areas,[32,39] whereas DLPFC μ-opioid activity as measured by PET imaging negatively correlates with the magnitude of anticipation of pain relief.[34] In Figure 1, significant regions identified in PET and functional magnetic resonance imaging studies have been delineated.

More recently, placebo analgesia has been framed as a form of reward anticipation response that acts to modulate one's experience of a particular stimulus. Imaging evidence has been found to support the involvement of both opioidergic and dopaminergic neural systems in this model.[22,40,41] Expanding on these investigations, Hall *et al.*[42] performed one of the most methodical genetic investigations into the placebo effect to date. From a sample of 262 participants with IBS, 112 individuals were genetically screened for two SNPs (rs4633 and rs4680). The functional polymorphism rs4680 results in an amino-acid change from valine to methionine (position 108/158) that decreases the activity of catechol-*o*-methyl transferase (COMT). COMT is a dopamine catabolizing enzyme critical in the prefrontal cortices and the presence of the Met allele of rs4680 results in significantly decreased enzymatic activity.[43] COMT activity has been suggested to influence areas such as cognitive performance,[44] personality traits[45] and reward processing.[46] Patients were randomized to one

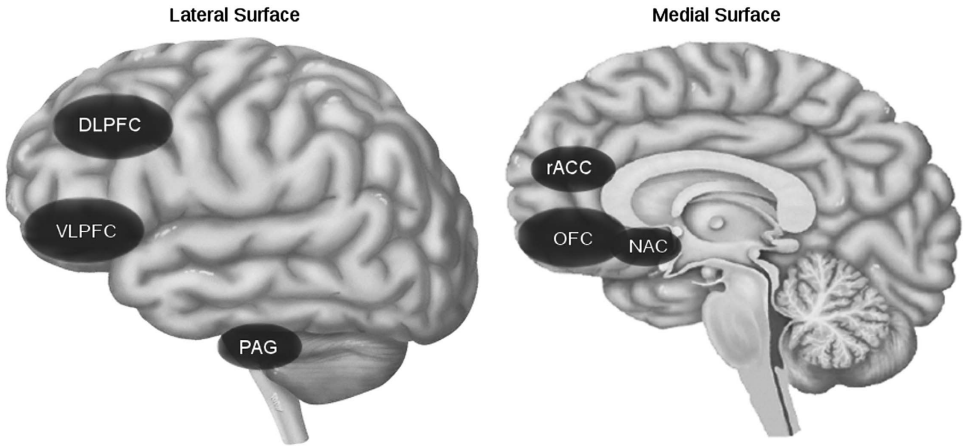

Figure 1. Regions of interest replicated in studies of placebo analgesia. Adapted from Stewart *et al.*[130] DLPFC, dorsolateral prefrontal cortex; NAC, nucleus accumbens; OFC, orbitofrontal cortex; PAG, periaqueductal gray; rACC, rostral anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex.

of three groups: (1) wait-list group, (2) limited placebo group or (3) augmented placebo group. The often neglected wait-list group provides a control for spontaneous remission that can be a substantial contributor to the placebo response.[47] The limited and augmented placebo groups served to modulate patient expectations with the augmented placebo group receiving the optimal practitioner–patient relationship. Patients homozygous for the low activity Met allele of COMT overall had greater symptom improvement based on changes in IBS-Severity Scoring System (IBS-SSS) score. More importantly, a statistically significant gene–environment interaction was found; patients with homozygous Met allele experienced significant symptom improvement with enhanced patient–practitioner interaction while Val/Val genotype experienced no statistical effect in different therapeutic environments.

Although a variation in COMT lends further support for the importance of the role of dopamine in placebo analgesia, the way in which rs4680 complements imaging studies is not immediately clear. Dopamine (DA) activity in reward processing structures is mainly regulated by dopamine transporters, not COMT. However, COMT activity has its greatest effect on dopamine in prefrontal regions, such as the DLPFC, VLPFC and OFC, which are frequently identified in functional magnetic resonance imaging studies of the placebo effect. Investigators have found that one's COMT genotype explains a significant amount of DLPFC and limbic system blood-oxygen level-dependent signals, with the Met COMT allele associated with greater activation in response to unpleasant visual stimuli.[48] The DLPFC has been described as the entry point of motivated behavior via its activation in anticipation of reward, which is consistent with DLPFC activation during anticipation of pain relief.[32,39,49] In addition, attentional bias also has a reported association with greater dopamine activity in the DLPFC.[50] These results from literature support the finding of a potential role of COMT in the placebo effect.

Further investigation into the impact of polymorphisms on the interaction between dopaminergic and opioidergic systems has been undertaken with the common SNP rs6265 (Val66Met) in the BDNF human gene and [^{11}C]-raclopride PET imaging.[51] It was postulated that Met carriers would have reduced activity-dependent BDNF granule release,[52] which could impact the dopaminergic neurons in reward-processing pathways.[53,54] A small sample of 49 healthy volunteers (11Met carriers and 38 Val/Val) had expectations modulated by a standardized statement leading them to believe that they would receive an experimental analgesic. During a somatic pain challenge before placebo administration Met carriers were found to have greater DA activity in the NAC bilaterally. Interestingly, the level of NAC dopamine activity positively correlated with subjective pain ratings and a mediation analysis provided evidence that this correlation was modulated by Met carrier status. During placebo administration, the DA activity in the NAC was significantly different between Met carriers and Val homozygotes; however, during this stage of the experiment, subjective pain ratings did not correlate with NAC DA activity. Although this meant that a genotype effect of rs6265 on placebo response could not be realized. This study demonstrated a measurable difference between BDNF genotypes in the quantity of NAC $D_{2/3}$ receptors, in the level of DA activity in response to pain and in response to anticipated pain relief. These important findings argue in favor of the hypothesis that the Met allele confers lower DA tone as well as lower DA response to reward. Without concomitant imaging with a μ-opioid radiotracer, it is not clear why in this instance a difference in placebo effect was not observed.

A more recent study by Peciña *et al.* investigated the influence of the SNP rs1799971 (A118G; asparagine (Asn) to aspartic acid (Asp), Asn40Asp) in OPRM1 on placebo analgesia.[53] Studies suggest that G carriers express fewer μ-opioid receptors, which results in decreased antinociceptive response to exogenous opioids.[55,56] A sample of 50 healthy volunteers underwent PET imaging with [^{11}C]raclopride and [^{11}C]carfentanil at baseline, during a somatic pain challenge and during somatic pain with the administration of a placebo. Expectations were modulated with standardized statements that lead participants to believe that the placebo was actually a potential medication capable of relieving pain. Consistent with the hypothesis, OPRM1 G carriers had lower expression of μ-opioid receptors in regions previously implicated in pain and emotional processing.[53,57] However, in response to pain without placebo, G carrier status was not correlated with pain threshold or opioid activity. In contrast, $D_{2/3}$ receptor activity in the NAC was significantly lower although it was uncorrelated with pain rating. Such a finding is inconsistent with the relationship between pain perception and G carrier status identified by others.[58] Although examining placebo-induced neurotransmitter changes, Montreal Pain Questionnaire (MPQ) sensory and affective pain measures correlated with μ-opioid but not $D_{2/3}$ activity in the NAC. This is supported by a similar study that demonstrated the same correlation with opioid activity.[41] However, the current study failed to demonstrate any correlation between pain severity and ACC opioid activity or NAC $D_{2/3}$ activity, which have been repeatedly identified.[34,35,41] G carriers were found to have lower opioid activity in the NAC, PAG, aINS, thalamus, regions repeatedly identified as playing a significant role in placebo analgesia,

although this did not translate into a significant separation in placebo responsiveness based on genotype. Methodologically, this study is a prototype for future studies seeking to disentangle the relationship between the placebo response, neurologic activity and genetics. Sufficiently similar findings with the established literature support a possible role of OPRM1 A118G in the placebo effect, although a more precise description of its role will rely on future studies of this mutation as well as others in key proteins of the opioidergic system.

Beyond the dopamine–opioid interaction in placebo analgesia, the endocannabinoid system has been found to impact the placebo response in patients conditioned with non-opioid analgesics.[29] Endocannabinoids have been extensively studied for their role in analgesia[59] and reward processing[60] and specifically for their interaction with the opioidergic system.[61] A recent genetic study of placebo analgesia incorporates PET imaging to specifically examine the impact of the rs324420 (C385A) functional mutation that has a significant impact on endocannabinoid degradation.[62] Specifically, rs324420 results in a Proline (Pro) to Threonine (Thr, position 129) missense substitution in fatty acid amide hydrolase reducing its catabolic activity of endocannabinoids. In this study, 42 participants underwent a painful stimulus (that is, hypertonic saline in masseter) with and without a placebo (that is, IV normal saline) while being led to believe that the therapeutic solution would have analgesic effects. The participants were analyzed as two groups: Thr129 carrier or Pro/Pro. Both groups displayed statistically similar μ-opioid and $D_{2/3}$ receptor activity for the same relative level of pain without a placebo. However, after a placebo was administered, Thr129 carriers experienced a large placebo response in all metrics of the Montreal Pain Questionnaire, which correlated with increases in μ-opioid receptor activity in many structures identified by previous placebo analgesia imaging studies (DLPFC, rostral anterior cingulate cortex, thalamus, NAC and insula).[34,41] The results of this study are very intriguing and contribute to the base of evidence for a genetic component to the placebo effect. Due to the fact that endocannabinoid activity was not directly measured, it is difficult to interpret why reduced analgesia was experienced in Thr129 carriers, which is contrary to findings in animal studies.[63] In fact, fatty acid amide hydrolase knockout mice display CBR1-dependent pain reduction and increased levels of endocannabinoids.[63,64] It is possible that the reconciliation of this discrepancy is due to fundamental differences in mouse and human neuroanatomy. This study provides the foundation for future genetic-imaging studies that should attempt to elucidate the dynamics of endocannabinoid and μ-opioid activity as it relates to conditioned placebo analgesia.

THE PLACEBO EFFECT AND SCHIZOPHRENIA

Placebo responder phenotype characteristics

The placebo response in schizophrenia is of growing concern as of late due to large clinical trial failures.[6,65] Unfortunately, the majority of studies of placebo response in antipsychotic drug trials focus on identifying study characteristics related to an increased response rate rather than placebo phenotype characteristics.[66–69] A meta-analysis examining studies from 1970 to 2010 found shorter trial duration to be associated with placebo response and a follow-up meta-analysis replicated the observation of increased placebo response rate in placebo-controlled randomized controlled trials (RCTs) since 1960.[68,70] In addition, placebo response has been found positively correlated with study sample size but not with the number of scheduled visits in RCTs.[71] In terms of patient or disease-related factors, younger age, greater baseline severity and shorter illness duration have been associated with increased placebo response.[68] Two meta-analyses consistently were unable to find sex to be predictive of placebo response, which is inline with the phenotypes of placebo analgesia and anxiolysis.[72,73] Although estrogen is being studied as an adjunctive medication in schizophrenia, this lack of differentiation of placebo response based on sex suggests that it is less likely that estrogen is an influential hormone in the neurobiology of placebo response in schizophrenia.

There is evidence to suggest that the temporal profile of response can be a trait used to distinguish treatment responders from placebo responders. In one retrospective analysis, Marques *et al*.[74] found that responses could be categorized in four ways: dramatic responders, responders, partial responders and non-responders. Unfortunately, ~70% of patients in placebo or active treatment groups were responders or partial responders (that is, responded with the same temporal profile). The only significant difference was observed with dramatic responders; only patients receiving active treatment were dramatic responders. This result, while based on only a small number of studies, suggests that placebo responders are more likely to respond late in the course of treatment. Although this result provides motivation for further investigation others to date have not identified such a temporal signature.[75]

Neurobiology and genetic studies

To the best of our knowledge, studies have not been conducted to investigate the neurobiology of the placebo effect in schizophrenia. However, based on the consistent trend that the placebo effect works through disease-specific mechanisms,[76] it is plausible that the relief offered by placebo treatment in schizophrenia modifies the dopaminergic tone of mesolimbic and mesocortical systems, which are responsible for the characteristic positive and negative symptoms of schizophrenia. Evidence that the placebo effect can recruit dopaminergic systems has been demonstrated in other medical conditions such as pain and Parkinson's disease, using PET imaging.[41,77] In addition, COMT, a dopamine catabolizing enzyme that exerts most of its influence in frontal regions, has been implicated in placebo responding patients with major depressive disorder[78] and IBS.[42] Future imaging genetic studies focusing on key genes in dopaminergic functioning would provide the foundation needed to understand the recent trend of increasing placebo response.

THE PLACEBO EFFECT AND ANXIETY

Placebo responder phenotype characteristics

The placebo response in the setting of anxiety strongly varies among anxiety disorder subtypes. Patients with obsessive compulsive disorder have consistently been shown to have a small or even absent placebo response while studies of treatments for panic disorder have a notably high placebo response.[79,80] Sociodemographic patient characteristics (for example, age, sex, social status, work status) have not been found to predict placebo response in panic disorder[73,81] or social anxiety disorder.[82] Similar to depression, as discussed later, the most reproduced patient characteristic investigators have found to associate with placebo responders is lower initial illness severity.[83–85] The temporal pattern of placebo response appears to be early and sustained in placebo anxiolysis, which differs with reports of placebo response patterns in depression.[73,86]

The study of the responder phenotype in placebo anxiolysis has been somewhat complicated by discrepancies in placebo response related to outcome measures. Early investigations into differences between drug-treated and placebo-treated individuals with panic disorder have found placebo anxiolysis to be effective at decreasing somatic symptoms of anxiety (for example, panic attacks), while less effective at influencing emotional aspects.[87,88] The Hamilton Anxiety (HAM-A) questionnaire used to differentiate placebo response from medication response is biased toward the

Table 3. Predictive variables of placebo phenotype in depression

Characteristic	*References*	*N*
Sociodemographic characteristics		
Sex (female)	Wilcox *et al.*[99]	197
	Cohen *et al.*[131]	2533
	Katon *et al.*[105]	99
Marital status (married > widow > single)	Wilcox *et al.*[99]	197
Age (older)	Wilcox *et al.*[99]	197
Age (younger)	Entsuah and Vinall[98]	1651
Race (non-Caucasians)	Cohen *et al.*[131]	2533
NEO neuroticism (lower score)	Katon *et al.*[105]	99
Education (fewer years)	Katon *et al.*[105]	99
Information-processing speed (higher)	Leuchter *et al.*[102]	26
Characteristics of depression		
Baseline severity: HAMD (lower)	Khan *et al.*[132]	2736
	Stein *et al.*[133]	738
	Papakostas and Fava[97]	13 107
	Entsuah and Vinall[98]	1651
	Brown *et al.*[104]	241
	Wilcox *et al.*[99]	197
	Bialik *et al.*[109]	99
	Katon *et al.*[105]	96
	Cohen *et al.*[131]	2533
'Late insomnia' item score of HAMD (higher)	Leuchter *et al.*[102]	26
Baseline severity: CGI-severity (lower)	Cohen *et al.*[131]	2533
Depression subtype (reactive)	Brown *et al.*[104]	241
Prior psychiatric treatment (less)	Brown *et al.*[104]	241
Prior use of antidepressants (none)	Brown *et al.*[104]	241
Experience with prior treatment (successful)	Brown *et al.*[104]	241
Illness duration (shorter)	Fairchild *et al.*[100]	55
	Brown *et al.*[104]	241
	Cohen *et al.*[131]	2533
Illness duration (longer)	Wilcox *et al.*[99]	197
Non-endogenous symptoms (present)	Fairchild *et al.*[100]	55
History of abusive disorders (positive)	Fairchild *et al.*[100]	55

Abbreviations: CGI, Clinical Global Impression; HAMD, Hamilton Depression Scale; NEO, neuroticism, extroversion, openness. N refers to the number of patients in the placebo group of each study.[130]

measurement of somatic expressions of anxiety and underemphasizes the emotional aspects, thus leading to seemingly indistinguishable results between placebo and drug treatments. However, alternative outcome measures, such as Quality of Life Enjoyment and Satisfaction, provide statistically significant differences between placebo and drug treatment owing to their broader scope.[88] A similar issue has been described with using the percentage of patients that are panic free as an outcome measure as it is uninfluenced by residual anticipatory anxiety and phobic avoidance.[87] Therefore, future works in placebo anxioloysis should be specifically cognizant of the outcome measures used to classify response while trying to identify specific phenotypic traits.

Mechanisms and genetics of placebo anxiolysis

Brain imaging studies of individuals undergoing placebo anxiolysis are relatively lacking. The underlying source of anxiety has been traced to the hyper-responsivity of the amygdala and response to treatment is often, but not always, associated with a decrease in responsivity.[89] Petrovic *et al.*[90] purport that placebo anxiolysis, like placebo analgesia, is an example of reward processing with expectations of reduced anxiety in placebo responders associating with increased activity in the OFC, ACC and VLPFC. In addition, self-reported relief positively correlated with activity in modulatory regions (that is, ACC and VLPFC) and negatively correlated with activity in perceptory regions (that is, extrastriate cortex and amygdala). Similar changes in amygdala activity have been observed using [H_2O^{15}] PET imaging in placebo-treated patients with social anxiety disorder. Decreased regional cerebral blood flow (rCBF) was observed in the left basomedial, left basolateral and right ventrolateral amygdala in those who responded to placebo relative to those who did not respond. In addition, a comparison of rCBF changes between SSRI and placebo responders found their neurophysiological changes to be indistinguishable.[91] A follow-up analysis examining fronto-amygdala coupling found remarkably similar co-activation patterns in placebo responders and SSRI responders, with increased DLPFC and rostral anterior cingulate cortex activation correlating with negative amygdala activity. This result lends support to the hypothesis that the neurobiological mechanisms of the placebo effect overlap with those of active medications.[92]

A substantial contribution to our understanding of the molecular basis of placebo anxiolysis has been made by combining genotyping with [H_2O^{15}] PET imaging.[82] A relatively small sample of 24 patients with social anxiety disorder from two RCTs underwent genotyping of the serotonin transporter length polymorphism region (5-HTTLPR) and tryptophan hydroxylase-2 (TPH2) G-703T polymorphism (rs4570625). Both of these genes are pivotal in the proper functioning of the serotonergic system and have polymorphisms that result in a hyperexcitable amygdala. Specifically, individuals with the 5-HTTLPR s/s genotype and TPH2 T-allele carriers display greater amygdala responsivity compared with other genotypes under similarly stressful situations.[93,94] The investigators found that decreased rCBF to the left amygdala was associated with placebo responders and that participants with the 5-HTTLPR l/l genotype displayed significantly reduced rCBF to the amygdala compared with the l/s or s/s genotypes ($P = 0.004$). As well, individuals with the TPH2 G/G genotype had significantly reduced rCBF to the amygdala compared with the G/T or T/T alleles and as a result, dominated the group of placebo responders. In addition, individuals with both l/l 5-HTTLPR and G/G TPH2 genotypes displayed the strongest placebo response. Surprisingly, rCBF in regions typically modulated in placebo analgesia, namely the ACC, OFC, DLPFC and VLPFC, did not display any difference in rCBF between placebo responders and non-responders.

Although these findings are an excellent step in the direction of uncovering the genetic underpinnings of the placebo effect, there are barriers to the full adoption of these results. Multiple factors in RCT design have been shown to influence placebo response rates in other diseases[67,95,96] as well as anxiety disorders.[85] When merging the data from multiple RCTs, it is very difficult to ensure similar environmental cues are held constant across the entire sample. For example, the two RCTs used by Furmark *et al.*[82] had different probabilities of randomization to placebo control. A link between higher probability of randomization to placebo and lower placebo response is thought to occur due to decreased expectation of improvement.[97] Future studies should take differences between RCTs into account when analyzing the placebo effect.

THE PLACEBO EFFECT AND DEPRESSION

Placebo responder phenotype characteristics

The placebo responder phenotype in depression has been extensively studied in the effort to reduce placebo response in clinical trials. A summary of sociodemographic and disease traits that have been studied for their predictive ability of placebo response is provided in Table 3, and unfortunately few traits have

strong evidence. Three reports could be found supporting a correlation between age and placebo response. In a study-level meta-analysis of 18 double-blind, placebo-controlled trials of venlafaxine, age <40 years was associated with a significantly higher placebo response.[98] Closer examination of these studies reveals that patients under 18 were not included, and patients older than 65 years were either not included or poorly represented. Wilcox *et al.*[99] performed a patient-level meta-analysis of four studies that found a trend toward increased placebo response among those >60 years old, although patients over 60 made up 7.1% of the sample. Studies with evidence that contradicts this association were either underpowered or did not compare placebo response at various age bins.[100–103] Brown *et al.*[104] performed the most balanced investigation of age in a pooled analysis of three studies to yield no variation in placebo response rate with age.

At this time, the literature does not support an association between gender and placebo response. Two small studies found females to be more responsive to placebos and a large meta-analysis of children and adolescents including 27 RCTs found a trend toward the positive correlation between placebo response and proportion females in the studies.[99,105] An equally strong group of studies do not find any association with gender.[98,102–104] Other traits such as marital status, education, race and NEO neuroticism have also been studied although not enough studies exist to warrant interpretation of these results.

In terms of major depressive disorder (MDD) characteristics among placebo responders, the most notable trend in the placebo response rate is that patients with a lower baseline severity of depression are more likely to respond to placebo compared with more severely depressed patients.[106] This finding has been consistently reproduced and provides one of the strongest predictive measures used in forecasting models of placebo response.[107,108] However, active medication response is relatively stable across levels of depression, which is why increasing the minimum Hamilton Depression Scale score has been recommended as a means of improving clinical trial performance. At this time, only three studies of illness duration have an adequate sample size to interpret results and unfortunately, no consensus exists based on length of current depressive episode or number of previous episodes.[98,104,109] Other MDD-specific traits such as associated sleep disturbance or anxiety have been studied although the body of literature is too nascent at this time to base judgements.

Perhaps a lack of associable characteristics among placebo responders is due to the reliability and/or consistency of the response. It seems logical that if placebo responders reliably respond to a placebo, they could be identified during the single blind run-in period of RCTs and simply excluded, thus decreasing the placebo response rate and increasing drug–placebo differences. A meta-analysis of 42 trials (SSRIs vs placebo) comparing trials that excluded placebo responders with those that did not exclude placebo responders, found no statistical difference in the effect size of treatment.[110] In addition, earlier studies with similar objectives found that drug and placebo response rates were not affected by this practice.[111,112]

Investigators have also examined the temporal pattern in placebo responders with MDD as phenotypic trait. Katz *et al.*[113] found that while the mean time to response was 13 days among SSRI-treated patients, placebo-treated patients required 16 to 42 days. This finding is supported by others that have described early symptom improvement to be twice as likely in antidepressant groups as placebo groups.[114] A robust response to antidepressants has been associated with early symptom relief. Such a claim also appears true for placebo treatment of MDD as successful statistical models have been developed to identify placebo responders based on percentage change of HAMD-17 score at week 2.[107]

Although efforts to identify phenotypic traits of placebo responders have been relatively unyielding, the development of the sequential parallel comparison design has led to a promising practical solution to reduce placebo response as well as required sample size.[115] The study design involves the enrichment of placebo non-responders from the first stage of the study, who then continue into the second stage. Drug efficacy is calculated based on both stages of the study; a recent implementation of sequential parallel comparison design demonstrate its strength in decreasing placebo response.[116]

Mechanisms and genetics of placebo in depression

Consistent with the placebo response in pain and anxiety, prefrontal regions have a prominent role in the resolution of MDD with placebo treatment. In an early study, prefrontal cordance, an electroencephalogram-derived biomarker of cortical blood flow, was seen to increase in placebo responders compared to non-responders.[117] Other investigations have found placebo responders and medications responders share the same pattern of increased activation in the prefrontal cortex, posterior insula and posterior cingulate, while displaying decreased activation in the subgenual cingulate, parahippocampus and thalamus as measured by (^{18}Fluodeoxyglucose) PET imaging. The considerable similarity in alterations to glucose metabolism seen in both placebo responders and medication responders argues strongly for a shared pathway involving serotonin.

Evidence for a role of the serotonergic system was revealed in recent investigations into the genetics of placebo response, which examined candidate genes in the monoaminergic systems and HPA axis for response to placebo ($n=257$) as well as bupropion ($n=319$) in patients diagnosed with MDD.[118] Genetic associations with placebo response or remission were found in the serotonin transporter (5-HTT), monoamine oxidase A (MAO-A) and serotonin 2A receptor (HTR2A). The strongest genetic association with placebo response or remission was observed with the A-allele of SNP rs4251417 in 5-HTT. Although this genetic association has not been observed in any other genetic studies of placebo response, the authors hypothesize that the relevance of this SNP could be linked with the 5-HTTLPR.[82] Other important SNPs that displayed nominal association with placebo response or remission include rs6609257, which is 6.6 kb downstream of MAO-A gene and rs2296972 in HTR2A. The functional significance of rs6609257 in MAO-A regulation is currently unknown; however, the results of other studies suggest an important role of MAO-A regulation via the minor allele of rs6323 and the placebo response.[78] MAO-A involvement is further supported by the nominal association of placebo response with rs2235186, which is in complete linkage disequilibrium with rs6323. MAO-A modulates serotonergic tone and serotonin has a demonstrated role in the reward pathway.[119] The last major finding relevant to the study of placebo was the association of HTR2A variant rs2296972 with placebo remission. This trend is important because it argues in favor of placebo effects working through mechanisms shared by the active medication of a treatment; SNPs in HTR2A have been associated with response to bupropion[118] and (es)citalopram[120,121] among others. However, SNP rs2296972 that displays nominal association with placebo remission in this study is not described as having association with antidepressants. It is possible that the HTR2A SNPs associated with antidepressant response and placebo response share a functional variant although that has yet to be demonstrated.

An earlier study of placebo response in the setting of MDD specifically examined the Val158Met COMT polymorphism and the Fnu4HI G/T polymorphism in MAO-A (rs6323) for association with the placebo response in 52 patients.[78] The investigators found that homozygous patients or carriers of the rs6323 T-allele were more likely to respond to placebo (47% and 50%, respectively)

than G-allele homozygotes. Patients with the rs6323 T-allele have been associated with greater emotional reactivity to their environment and greater interpersonal hypersensitivity.[122,123] This finding is congruous with the repeatedly demonstrated ability of environmental cues to modulate patient expectations and the magnitude of placebo response. In the case of COMT, patients with the high activity form of COMT (Val–Val) were found to have the highest placebo response. This finding lends support to the involvement of COMT in the placebo response; however, it is the exact opposite genetic finding to that of placebo analgesia.[42] Interestingly, individuals with the high activity form of COMT have been found to have a stronger μ-opioid response to painful stimuli[124] and larger releases of dopamine in the nucleus accumbens in response to a reward,[125] making a case that individuals with high COMT activity could be more likely to respond to placebo. The role of endogenous opioid activity in depression is an active area of research, with recent studies suggesting a role in the regulation of brain-derived neurotropic factor, which is a central component to the pathology of depression.[126,127] However, given our limited understanding of neural mechanisms in placebo treatment of depression, such speculations are at best tenuous.

Beyond the theoretical limitations of not including a no-treatment control, the methodological choice to combine different RCT samples reduces the sensitivity of these placebo genetics studies. A higher probability of receiving placebo has been correlated with a lower placebo response presumably due to lowered expectations of improvement.[97,128,129] Leuchter *et al.*[78] used patients from four different clinical trials, one of which randomized 75% of participants to placebo, while the other three had a 50% chance of receiving a placebo. Similar heterogeneity is observed among the clinical trials included by Tiwari *et al.*,[118] although the use of a conditional logistic regression model corrected for sociodemographic variables as well as the specific trial would have partly accounted for the heterogeneity. Few studies have investigated the role of genetic factors in placebo response in MDD and those that presently exist have been restricted to traditional candidate genes. Genome-wide hypothesis-free studies in larger samples are required to truly understand the role of genetic factors in placebo response.

RECOMMENDATIONS AND FUTURE DIRECTIONS

Investigations into the placebo effect are growing in number and with good reason; the placebo effect is a phenomenon with the potential to provide extraordinary insight into the process of healing. Althouggh research into the placebo effect has been studied extensively at the level of brain imaging, genetics and other molecular methods (for example, metabolomics) have yet to be fully implemented in this field. In general, the genetic studies presented in this review provide complementary evidence as well as a new lens through which to scrutinize current models of the placebo effect. The genetic-imaging studies have generally focused on analyzing single polymorphism from a gene of interest. In the future, it would be interesting to see how gene–gene interaction (for example, OPRM1 and fatty acid amide hydrolase) contribute to placebo effect.

Moving forward improvements in study design are warranted to improve the sensitivity of genetic studies and to ensure results are reproducible. Current genetic studies in general are limited due to a lack of no-treatment control groups (except for Hall *et al.*[42]), using samples with heterogeneous therapeutic experiences, and relatively small sample sizes. Without question the most important recommendation for future genetic investigations is the inclusion of a no-treatment control group as the interpretation of findings will always remain tenuous without such a measure. Given the ethical dilemma surrounding the use of placebo-control groups in RCTs, the path to including no-treatment control groups in future studies is unclear.

Future genetic investigations would yield more impactful findings by interrogating a larger number of genetic variants while concomitantly performing imaging. Although incorporating more genetic targets does exacerbate the issue of multiple comparisons, such studies would provide a broader context with which to interpret findings. The combination of imaging with genetics would ensure that future genetic studies do not yield insular findings in the overwhelmingly imaging-dominated field of placebo research. Improving on the weaknesses in current placebo genetics research highlighted in this review, genetics is poised to add significant clarity to an intriguing yet enigmatic phenomenon.

CONFLICT OF INTEREST

R.D.H and A.K.T have no conflicts of interest to declare. J.L.K. has been a consultant to GSK, Sanofi-Aventis and Dainippon-Sumitomo and received honoraria from Eli Lilly.

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