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Neural and psychological predictors of treatment response in irritable bowel syndrome patients with a 5-HT_3 receptor antagonist: a pilot study

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SUMMARY

Background
Symptom improvement in irritable bowel syndrome (IBS) treatment trials varies widely, with only 50–70% of patients qualifying as responders. Factors predicting treatment responsiveness are not known, although we have demonstrated that symptom improvement with the 5-HT_3R antagonist alosetron is correlated with reduced amygdala activity.

Aim
To determine whether neural activity during rectal discomfort or psychological distress predicts symptom improvement following treatment with alosetron.

Methods
Basal psychological distress and neural activity (^{15}O PET) during uncomfortable rectal stimulation were measured in 17 nonconstipated IBS patients who then received 3 weeks of alosetron treatment.

Results
Greater symptom improvement was predicted by less activity in bilateral orbitofrontal cortex (OFC) and medial temporal gyrus during pre-treatment scans. Lower levels of interpersonal sensitivity predicted greater symptom improvement and were positively related to activity in left OFC. Connectivity analysis revealed a positive relationship between activity in the left OFC and right amygdala.

Conclusions
Irritable bowel disease symptom improvement with 5-HT_3R antagonist alosetron is related to pre-treatment reactivity of the left OFC, which may be partially captured by subjective measures of interpersonal sensitivity. The left OFC may fail to modulate amygdala response to visceral stimulation, thereby diminishing effectiveness of treatment. Psychological factors and their neurobiological correlates are plausible predictors of IBS treatment outcome.

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INTRODUCTION

With an estimated prevalence rate of 10–15% in industrialized countries, irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders.[1] Patients with IBS report a profound impairment of health-related quality of life[2–4] and generate over $30 billion in healthcare costs each year in the US.[5] Despite the reported effectiveness of a variety of lifestyle-based, psychological[6] and pharmacological treatments,[2, 7] overall treatment success remains unsatisfactory for both patients and physicians. Inconsistent responses to therapy may be partially related to the heterogeneity of patients in terms of their pathophysiology, psychological comorbidity, gender and other factors, including genetic polymorphisms.[8] It would therefore be advantageous to identify prognostic markers that distinguish patients likely to benefit most from specific forms of treatment. Such an approach would streamline the therapeutic process, thereby increasing patient satisfaction and reducing healthcare utilization. Moreover, the cost effectiveness of demonstrating treatment effects in clinical trials would be greatly enhanced, if the study population were restricted to patients with similar pathophysiology.[9] Despite the potential benefit, the development of IBS patient profiles predictive of a therapeutic response to a particular treatment has received little empirical attention.

Several large clinical trials have demonstrated that serotonin receptor (5-HT_3R) antagonists are among the most effective therapeutic options to date for both male and female diarrhoea predominant-IBS patients (IBS-D[10–13]). Currently, alosetron is the only 5-HT_3 antagonist approved by the US Food and Drug Administration (FDA) for the treatment of severe IBS-D in women. Due to concerns of an association of alosetron with ischaemic colitis and serious complications of constipation,[14] alosetron is only indicated for the treatment of women with severe, chronic IBS-D (lasting longer than 6 months) who do not have anatomical or biochemical abnormalities of the gastrointestinal tract, and who have not responded adequately to conventional therapy and is therefore obtained through a comprehensive risk management plan.

5-HT_3R antagonists alleviate IBS symptomatology as assessed by a global endpoint ('adequate relief of IBS pain and discomfort'[15]) as well as specific IBS symptoms such as frequent bowel movements, feelings of urgency, and chronic abdominal pain and discomfort[16]. A recent meta-analysis assessing the efficacy of various IBS treatments on overall symptom improvement reported that 5-HT_3R antagonists led to a significant symptom improvement in 54–69% of IBS-D patients who were treated for at least 2 weeks.[17] This indicates that while 5-HT_3R antagonist treatment is beneficial for the majority of IBS-D patients, there is a sizable subset of patients who do not meet responder criteria. The profile of patients who are most responsive to this treatment remains unclear, as few studies have examined how pre-treatment characteristics relate to eventual symptom improvement.

The precise mechanisms whereby 5-HT_3R antagonists bring about therapeutic changes in IBS are incompletely understood; however, preliminary evidence suggests that both central and peripheral mechanisms may be involved.[13] Using ^{15}O positron emission tomography (PET), we previously reported that changes in brain activity over 3 weeks of treatment with the 5-HT_3R antagonist alosetron were associated with IBS symptom improvement in nonconstipated IBS patients.[18] In this randomized, placebo-controlled study, subjective symptom improvement was associated with reduced activity in the amygdala, a subcortical region of the limbic system that is more active during visceral stimulation in IBS patients than in nonpatients.[19] The human amygdala is rich in 5-HT_3Rs[20] and has anatomical and functional connections with raphe nuclei[21] and pontine structures,[22] which modulate serotonergic input to the nervous system and with prefrontal and orbitofrontal brain regions that modulate limbic system activation through top-down regulation.[23] Abnormal amygdala reactivity stemming from dysfunction in top-down or bottom-up neural inputs may produce similar gastrointestinal symptoms, while obscuring mechanistic differences relevant to determining the most effective treatment for a specific central deficit. Neuroimaging is ideally suited to identify the neural mechanisms underlying treatment responsiveness in IBS patients; however, the high costs associated with this technique make it impractical in a clinical setting.

A retrospective pilot study was conducted to test whether differences in pre-treatment brain activity predict eventual IBS symptom improvement with the 5-HT_3R antagonist alosetron. To identify potentially unique neural characteristics of more responsive patients, we used ^{15}O PET to measure the association between eventual symptom improvement and

pre-treatment brain activity during rectal distention, a laboratory procedure known to produce physical discomfort similar to IBS symptoms.[24] The second goal of the study was to obtain preliminary data describing the relationship between these neural characteristics and psychological distress, which could guide the development of a self-report measure that is optimized to predict symptom improvement with the 5-HT_3R antagonist alosetron in a clinical setting. Some of these results have been reported in abstract form.[25]

METHODS

Participants

The patients described in this study were participating in a double-blind, randomized, controlled trial comparing the efficacy of the 5-HT_3R antagonist alosetron with placebo. As the focus of this preliminary study is on predictors of improvement with alosetron, only patients who received alosetron were relevant for the current analyses. All patients met Rome I criteria for IBS[26] and were clinically and endoscopically without inflammatory or other structural intestinal disease and free of psychiatric disorder and clinically significant psychological symptoms. Before screening, all patients gave informed consent in compliance with FDA requirements. Patients were excluded during screening, if they had a major psychiatric disorder or clinically significant psychological symptoms. Patients discontinued peripherally acting IBS treatments 7 days before and centrally acting drugs 30 days prior to screening and for the duration of the study.

Of the 23 patients randomized to receive alosetron, 17 patients (nine female), were included in the present analyses. Patients were classified as diarrhoea-predominant (n = 11) or having alternating bowel habits (n = 6; symptoms of both diarrhoea and constipation), based on criteria published elsewhere.[27] Patients were excluded from analyses because of technical difficulties related to PET scanning (n = 4) and noncompletion of a daily symptom diary (n = 2). Patients included in the current analyses (I) and those who were excluded (E) did not differ in mean age (M_I = 39.59 years vs. M_E = 35.57 years), previous 6-month IBS symptom intensity and unpleasantness (M_I = 13.18 vs. M_E = 13.07; M_I = 12.22 vs. M_E = 11.21) or 24-h IBS symptom intensity and unpleasantness (M_I = 7.18 vs. M_E = 7.64; M_I = 6.28 vs. M_E = 6.07) as measured by 20-cm validated visual analogue scales (all Ps > 0.2).[28] No side effects were reported. As the goal of this study was to identify, prior to treatment, predictors of patients' response to active drug, this study does not include placebo vs. drug comparisons. Such comparisons and specific analyses of placebo response have been reported previously.[18, 29, 30]

Study outline

Following a 1-week pre-treatment screening period and prior to randomization, each patient completed a pre-treatment testing session which included a PET scan with visceral distension and administration of the Brief Symptom Inventory,[31] a questionnaire that measures various forms of psychological distress. Patients were then randomized to treatment with either alosetron 1 mg b.d. or placebo b.d. for 3 weeks. A daily symptom diary was completed during a 1-week pre-treatment screening prior to the pre-treatment testing session and then each day for the duration of study. Details of the clinical trial along with other features of this study have previously been reported.[18, 30]

PET scanning. PET scans were performed by dynamic imaging with a Siemens/CTI 953 tomograph (Siemens-Computer Technology, Inc., Knoxville, TN, USA), collecting 31 contiguous data planes corresponding to an axial depth of 3.375 mm each, in a 128 × 128 image matrix. Emission scans were reconstructed from projection data with calculated attenuation correction. After intravenous administration of 25 mCi ^{15}O-water, PET data were obtained during four 30-s frames, and summed for frames 2–4, which followed entry of tracer into the brain.

Rectal distention. A computer-driven pump (barostat) was used to inflate a balloon positioned in the rectum.[32] During the pre-treatment session, PET images were acquired during four time points: during a resting baseline and 1 min of moderate rectal distension (45 mmHg), as well as during a second resting baseline and moderate rectal distention, which occurred following acquisition of additional data (reported elsewhere[18, 30]). Rectal distension with 45 mmHg was previously identified as the highest level of pressure tolerated by all individuals in a large sample of patients with IBS.[33] As we sought to elicit moderate discomfort during PET scanning, we chose

to deliver a 45 mmHg inflation to ensure that the stimulus was below the threshold of tolerance for all patients.

Assessment and statistical analyses

Symptom improvement. To control for initial individual differences in IBS symptoms, symptom improvement was defined by per cent change in IBS symptoms from 1 week prior to the pre-treatment session to the final week of treatment.[29] IBS symptoms were measured using an index comprising the weekly product of three daily diary items that assessed frequency (how many times did you have abdominal pain or discomfort today?), severity (how severe was your worst episode of abdominal pain or discomfort today?) and duration (taking all of today's attacks of abdominal pain or discomfort together, how long did they last?) of IBS symptoms on a 0–10 scale.

Analysis of brain activity. Using statistical parametric mapping (SPM'99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK), images for each patient were first realigned to their initial image to correct for head motion, then normalized into standard stereotactic Montreal Neurological Institute space and smoothed with a 12-mm Gaussian kernel to increase the signal to noise ratio. Planned comparisons were then computed as linear contrasts for individual patients. The resulting contrast images were used in random effect analyses at the group level.

Neural response to rectal distension was computed by subtracting summed brain activity during resting baseline periods from summed brain activity during periods of rectal distention. Each patient's per cent symptom change was then entered into a 'simple regression' analysis in SPM to determine if extent of symptom improvement was related to variations in neural response to pre-treatment rectal distention. These group-level analyses were conducted with a significance threshold of $P < 0.001$ and extent threshold of 10 voxels.

Brain regions of interest (ROIs) that were predictive of symptom improvement were subject to functional connectivity analyses, which are used to determine if activity in other brain regions covary with activity in specified ROIs. While such analyses are correlational and thus do not determine causal or directional links between regions, they can help support hypotheses about the altered functioning of particular neural networks. Specifically, we were interested in how activity in brain regions predictive of symptom improvement is related to activity in the amygdala. Differences in signal intensity between baseline and rectal distension in ROIs were obtained for each patient. Using the same analytical strategy described for the initial PET scan analyses, these values were then entered in a simple regression analyses to determine if between-subjects variation in ROI activity was positively or negatively associated with activity in other brain regions. All ROIs were spherical regions (10-mm radius) centred at coordinates corresponding to the peak voxel of brain activity of interest.

Psychological distress. The Brief Symptom Inventory (BSI[31]) is a well-validated questionnaire that measures a variety of forms of psychological distress on standardized subscales (somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism), and provides a global symptom index of overall psychological health. As we were interested in the overlap between brain response to visceral stimulation and psychological distress, the relationship between activity in the previously defined ROIs and psychological distress that predicted per cent symptom improvement was tested. Differences in signal intensity between baseline and rectal distension in ROIs were obtained for each patient. These values were then correlated with levels of psychological distress.

RESULTS

Symptom improvement

Following 3 weeks of alosetron treatment, patients reported an average of 54% (s.d. = 66%, $P < 0.005$) improvement in IBS symptoms as assessed by the diary index. As demonstrated by the large standard deviation, patients experienced varying levels of symptom change with treatment (Figure 1). This suggests that, as expected, patients were differentially responsive to treatment. Symptom improvement did not differ across gender or predominant bowel habit (diarrhoea, alternating).

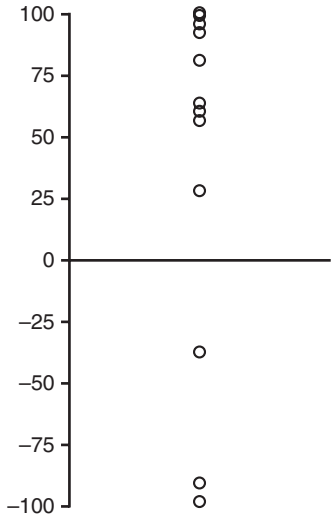

Figure 1. Per cent symptom change as measured by daily symptom diary.

Predictors of symptom improvement

Pre-treatment brain activity. Patients who reported higher levels of symptom improvement with alosetron had less distension-induced activity in bilateral orbitofrontal cortex (OFC) and the left medial temporal gyrus (MTG) prior to treatment (Table 1). Connectivity analyses were then performed to assess the relationship between activity in the ROIs predictive of symptom improvement and amygdala responsiveness to rectal distension. A positive correlation was observed between activity in the right amygdala (Figure 2) and the left OFC (20, −4, −20; $r = 0.51$, $P < 0.04$) such that patients with less activity in the left OFC during distension also had less activity in the right amygdala (Figure 3).

Table 1. Brain activations associated with visceral distension (vs. baseline) that predicted eventual irritable bowel disease symptom improvement

	Talaraich coordinates					
Region	*x*	*y*	*z*	Voxels	*T* score	*r*
Orbitofrontal cortex (BA 11)						
L	−24	34	−12	61	6.05	−0.84
R	28	38	−10	15	4.20	−0.74
Medial temporal gyrus (BA 21)						
L	−56	−56	2	22	4.44	−0.75

r values indicate the correlation between brain activity and eventual symptom improvement ($P < 0.001$, extent threshold of 10 voxels).

Psychological distress. Patients with lower levels of interpersonal sensitivity (e.g. 'My feelings are easily hurt') were more likely to report symptom improvement following 3 weeks of treatment with alosetron ($r = -0.49$, $P < 0.04$). A test of the relationship between interpersonal sensitivity and activity in ROIs predictive of symptom improvement revealed that patients with lower levels of interpersonal sensitivity had less distension-induced activity in the left OFC ($r = 0.69$; $P = 0.002$). Interpersonal sensitivity was not correlated with activity in other ROIs.

The relationship between interpersonal sensitivity, activity in the left OFC, and symptom improvement was further explored with multiple regression analyses to determine whether activity in the left OFC and interpersonal sensitivity predicted unique variance in symptom improvement. After removing variance explained by interpersonal sensitivity, activity in the left OFC still explained 77% of the variance in symptom improvement [$\Delta F(1,15) = 36.55$; $P \leq 0.001$]. Conversely, interpersonal sensitivity only explained 0.3% of the variance in symptom improvement after controlling for activity in the left OFC [$\Delta F(1,15) = 4.73$; $P \geq 0.07$]. The predictive value of interpersonal sensitivity may therefore be explained almost entirely by activity in the left OFC, while activity in the left OFC remained a strong predictor of symptom improvement over and above interpersonal sensitivity.

DISCUSSION

Treatment with the 5-HT_3R antagonist alosetron was more effective for nonconstipated IBS patients who exhibited less distension-induced activity in bilateral OFC and the left MTG at baseline. Connectivity analyses revealed a positive correlation between activity in the left OFC and the right amygdala. IBS patients with lower levels of self-reported interpersonal sensitivity were also more likely to improve with treatment, and to have less activity in the left OFC during rectal distension. Further analyses indicated that activity in the left OFC accounted for a large per cent of variance in symptom improvement independent of interpersonal sensitivity, suggesting that the predictive value of

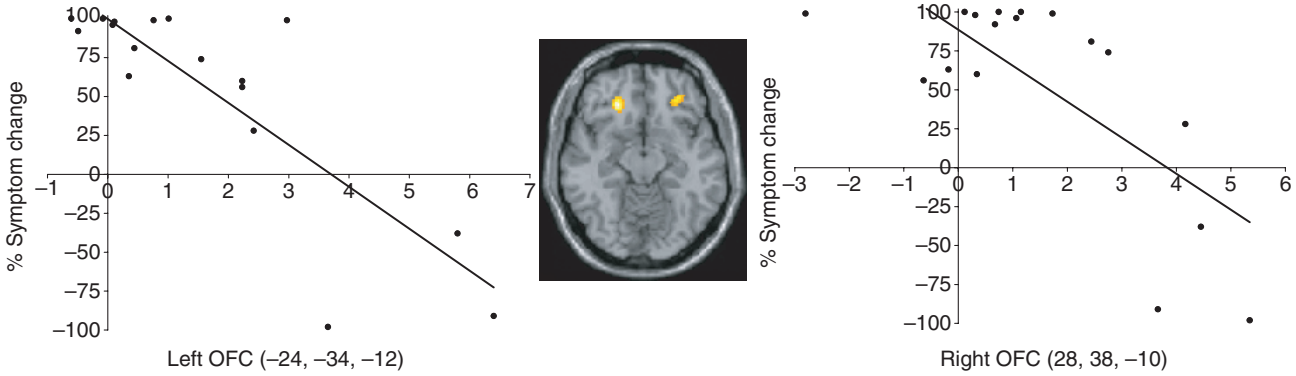

Figure 2. An SPM image and scatter plots showing increased activity in the left and the right orbitofrontal cortex (OFC) during rectal inflation relative to baseline that is negatively correlated with per cent symptom change. Each point on the scatter plots represents a single patient.

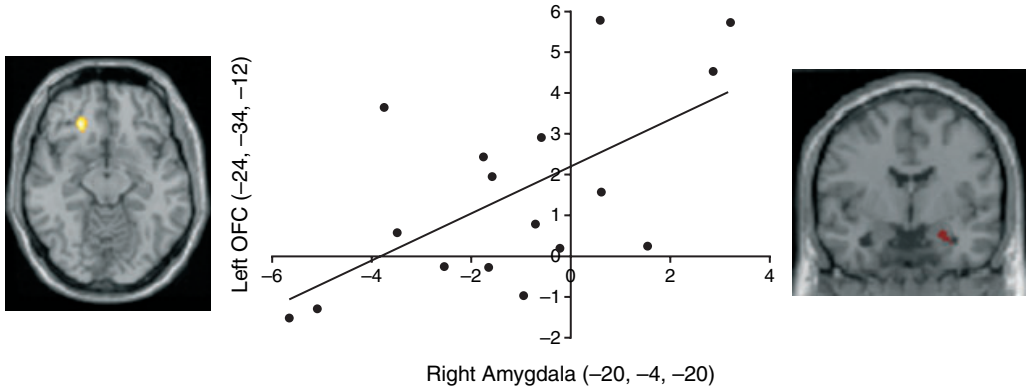

Figure 3. SPM images and scatter plot showing increased activity in the left orbitofrontal cortex (OFC) during rectal inflation relative to baseline that was negatively correlated with per cent symptom change and positively correlated with activity in the right amygdala. Each point on the scatter plot represents a single patient.

interpersonal sensitivity may be largely accounted for by activity in the left OFC.

As a potential mechanism contributing to the beneficial effects of 5-HT$_3$R antagonists on IBS symptoms is their inhibitory effect on the amygdala,[18] indirect influences on amygdala activity may affect therapeutic outcome. Given the robust functional[34] and anatomical[35] relationship between the OFC and amygdala, the hyper-reactivity in the OFC observed in less responsive patients, may upregulate the amygdala, thereby diminishing the effectiveness of 5-HT$_3$R antagonists. As such, patients with hyper-reactive OFC may be better served by pairing pharmacological treatment with a treatment known to normalize activity in the OFC. For example, patients with depression who receive cognitive behavioural therapy, but not those who receive pharmacological therapy alone, exhibit reduced OFC activity with symptom improvement.[36] Additional research is necessary to determine whether this finding extends to patients with IBS.

Activity in the left MTG was also associated with symptom improvement, but not with amygdala activity. MTG has been implicated in numerous cognitive functions including the retrieval of autobiographical memories.[37] Rectal distention may trigger the memory of previous IBS-related discomfort to a different degree across patients. Such memories may, in turn, increase patient sensitivity to normal visceral signals, thus creating a positive feedback loop that exacerbates symptoms, making patient symptoms more resistant to pharmacological treatments that do not directly affect normative visceral signals.

It may seem surprising that interpersonal sensitivity was the only psychological factor that predicted symptom improvement, and not anxiety, depression or somatization. These latter factors are more often associated with IBS symptoms.[27, 38, 39] However, in this study, we evaluated psychological factors which would predict treatment response, rather than identifying correlation of psychological factors and IBS symptoms. Compared with the general population, patients with IBS also have higher levels of interpersonal sensitivity,[39, 40] a dysfunction that may increase the likelihood of experiencing psychosocial stressors. Indeed, a large body of data indicates that psychosocial stressors play an important role in triggering first onset of IBS and exacerbating chronic symptoms. This suggests that IBS patients with the highest levels of interpersonal sensitivity may be most vulnerable to the deleterious effects psychosocial stressors have on their IBS symptoms. While our findings do not demonstrate a causal relationship between interpersonal sensitivity and IBS, they do suggest that interpersonal sensitivity may be a marker for central inhibitory dysfunction in general, and OFC responsiveness in particular, which is more directly associated with treatment efficacy. Depression, anxiety and somatization were not significantly correlated with brain activity in the left OFC. The OFC is implicated in social functioning, emotional intelligence[41] and self-conscious emotions.[42] Brain damage to this region results in reduced capacity to recognize negative social evaluations, such as disappointment and to express emotions such as embarrassment, shame and guilt.[42] Thus, one of the consequences of hyperreactivity or dysregulation of OFC may be a heightened sensitivity to social evaluation, which may have been captured to some degree by the interpersonal sensitivity scale of the BSI. The relationship between the left OFC and interpersonal sensitivity suggests promise for the development of self-reported diagnostic measures that serve as a proxy for patterns of brain activity most closely associated with treatment outcome. These self-report measures could then be used in clinical contexts to identify IBS patients who are less likely to respond to 5-HT_3R antagonist treatments.

As few IBS treatment studies have measured the relationship between neural activity and treatment outcome,[18, 30] it is difficult to discuss our current findings in the context of a large body of published research on this topic. There is, however, a growing literature aimed at identifying similarities and differences in neural activity in patients with IBS and healthy individuals during visceral stimulation (for an extensive review, see Ref. 43). These studies generally report a similar pattern of activations across groups, with IBS patients demonstrating a greater activity in brain regions associated with pain processing, including insula,[44] dorsal anterior cingulate[45, 46] and thalamus,[44, 47] and corticolimbic regions including infragenual cingulate cortex, amygdala and prefrontal cortex.[44, 48]

Limitations

This study was not prospectively designed to test the factors predicting outcome, but a *post hoc* analysis conducted to identify psychological constructs and activity in brain regions predictive of symptom improvement with 5-HT_3R antagonist treatment. These pilot data may play an important role in informing the design of future studies that specifically aim to predict eventual symptom improvement at the neural and psychological level by guiding selection of brain ROIs and development of psychosocial assessments. To this end, we do not suggest that the BSI is an optimal instrument for predicting IBS symptom improvement associated with specific brain circuit dysfunction; however, the relationship between these factors and interpersonal sensitivity does suggest a starting place for the development of an instrument optimized for its predictive capacity. Factor analyses among multiple psychosocial measures that have been administered to a large number of patients prior to treatment with a 5-HT_3R antagonist may reveal a latent variable that best predicts IBS symptom improvement associated with OFC dysfunction.

Results were obtained with a relatively small sample size and may not be generalizable to all patients with IBS or to treatment with alosetron in general. A larger sample size is also needed to determine whether interpersonal sensitivity and amygdala activity are only related to activity in the left OFC or if this apparent laterality is simply because of the relatively small number of patients studied. A similar determination should be made about the lack of association between activity in the left OFC and the left amygdala; however, activity in the right amygdala has been associated with automatic emotional processing more frequently than the left amygdala.[49]

Implications

Neuroimaging has the capacity to both predict the effectiveness of a drug to a better degree than most other physiologic outcome measures and help specify the central mechanisms by which a drug or other intervention exerts its beneficial effects. A better understanding of these central mechanisms will allow for greater individualization of treatments based patient characteristics. For instance, patients with certain psychological disturbances (and underlying neurobiological dysregulation) may be best served by cognitive behavioural therapy paired with pharmacological therapy, which may target a particular deficit more effectively than pharmacotherapy alone.

Additional research focused on identifying characteristics of IBS patients who are more responsive to different forms of treatment is warranted. Although this study was conducted in a relatively small sample and requires replication, these pilot data provide insight into the psychological and neural characteristics of IBS patients who are more responsive to treatment with 5-HT$_3$R antagonists and suggest that psychological factors and their neurobiological correlates are plausible predictors of IBS treatment outcome.

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