Clinical Note

Neural Predictors of Successful Brief Psychodynamic Psychotherapy for Persistent Depression

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Abstract

Background: Psychodynamic psychotherapy has been used to treat depression for more than a century. However, not all patients respond equally well, and there are few reliable predictors of treatment outcome. ***Methods:*** We used resting ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scans immediately before and after a structured, open trial of brief psychodynamic psychotherapy (n = 16) in conjunction with therapy process ratings and clinical outcome measures to identify neural correlates of treatment response. ***Results:*** Pretreatment glucose metabolism within the right posterior insula correlated with depression severity. Reductions in depression scores correlated with a pre- to posttreatment reduction in right insular metabolism, which in turn correlated with higher objective measures of patient insight obtained from videotaped therapy sessions. Pretreatment metabolism in the right precuneus was significantly higher in patients who completed treatment and correlated with psychological mindedness. ***Conclusions:*** Resting brain metabolism predicted both clinical course and relevant psychotherapeutic process during short-term psychodynamic psychotherapy for depression.

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Introduction

A cornerstone of treatment for major depressive disorder, psychodynamic psychotherapy has been continuously practiced since the late 19th century. An outgrowth of Freudian analysis, modern psychodynamic psychotherapy focuses on how past experience, including significant relationships, influences character and current relational styles. Psychodynamic treatment can generate insights that change affect and behavior. Meta-analyses of both long- and short-term psychodynamic therapies indicate their overall effectiveness for depression and related psychiatric disorders [1, 2]. However, as with other

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18–60 years	Active suicidal ideation
Major depressive disorder diagnosis confirmed by doctoral-level clinician using the Structured Clinical Interview for DSM-IV (SCID)	History of mania, psychosis, or obsessive compulsive disorder
	Current panic, substance, or posttraumatic stress disorder
	Unstable medical or neurologic illness
Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) score ≥12	Current use of other psychotropic medications (except occasional sleep aids)
Current depressive episode <5 years	Current treatment with individual psychotherapy
Current treatment with adequate dose of an SSRI, SNRI, or bupropion for ≥8 weeks and a stable dose for ≥4 weeks	>3 previous, adequate trials of psychotherapy that were considered unhelpful or unsuccessful by patient report

SSRI = Selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

treatments for depression, discontinuation rates for psychodynamic psychotherapy are high, and reasons for early termination are difficult to predict [3, 4].

Although understudied relative to other interventions [5], psychodynamically oriented therapies have been preliminarily associated with synaptic and metabolic changes in limbic, midbrain, and prefrontal regions [6]. However, heterogeneity of treatment (even within-study) and lack of discrimination between responders and nonresponders limit previous studies in the field. The present investigation used resting ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) to study individuals with incompletely treated major depressive disorder before and after a 16-week trial of adjunctive psychodynamic psychotherapy. We deployed a manualized treatment and obtained measurements of psychotherapy process by rating videotaped sessions using a validated metric. These methods ensured that treatment was standardized and reproducible and provided the opportunity to explore neural correlates of the psychotherapy process. We also compared pretreatment scans between individuals who completed versus discontinued treatment and evaluated ongoing therapeutic alliance and depression scores to explore predictive markers of treatment outcome.

Materials and Methods

Patients
Study procedures were Institutional Review Board approved and participants provided written informed consent. All procedures took place at a single academic medical center in Boston, Mass. Inclusion and exclusion criteria are summarized in table 1. Patients were paid for their participation in the imaging part of the study.

Psychotherapy Treatment and Process Measurement
Please refer to online supplementary material Supplemental Methods (for all online suppl. material, see www.karger.com/doi/10.1159/000364906) for a detailed description of the psychotherapy intervention and process measurement. Briefly, all participants received 16 sessions of weekly, individual psychotherapy using the Core Conflictual Relationship Theme (CCRT) manual [7], administered by 1 of 4 trained study therapists. The CCRT approach is based on the supportive-expressive model of psychodynamic psychotherapy. Treatment focused on eliciting 'relationship episodes' characteristic of a problematic, recurring interpersonal pattern (weeks 1–4); achieving insight by working through the patient's history and his/her interactions with the therapist (weeks 5–12), and consolidating gains (weeks 13–16). Participants were maintained on stable, adequate doses of antidepressant medication. Each session was videotaped, and 2 sessions per patient were rated for psychotherapy process using the Psychotherapy Process Q-Set (PQS) [8].

Clinical Measures
Patients were evaluated using the Hamilton Depression Rating Scale (HamD-17) [9] at the pretreatment visit, after therapy sessions 1, 2, 4, 10, and 16, and at a 3-month follow-up visit. At pretreatment, patients also completed the Psychological Mindedness Scale [10], which measures capacity for self-examination and personal insight. Immediately following therapy sessions at weeks 2, 4, 6, 8, 10, 12, 14, and 16, the patient and therapist independently completed the Working Alliance Inventory-Short Version, Revised [11], which assesses agreement on the tasks and goals of therapy and development of an affective bond.

PET Scans
Please refer to online supplementary material Supplemental Methods for a detailed description of PET image acquisition, preprocessing, and analysis. Briefly, resting ^{18}FDG scans (Siemens HR+) were acquired prior to the first therapy session and again within 7 days of completing treatment. Following image processing, voxel-wise tests identified clusters where pretreatment regional cerebral metabolic rate of glucose uptake (rCMRglu) co-varied significantly with depression severity (HamD-17). Follow-up tests determined whether metabolic changes after treatment correlated with change in HamD-17, as well as with specific PQS measures.

Table 2. Comparison of baseline patient characteristics in completer (n = 9) and noncompleter (n = 7) groups

	Mean	SD	t	p
Age, years				
Completers	41.1	11.2	1.15	0.27
Noncompleters	34.0	14.3		

	Males	Females	χ^2	p
Sex				
Completers	1	8	2.11	0.26
Noncompleters	3	4		

	Mean	SD	t	p
HamD-17				
Completers	19.9	3.8	1.40	0.18
Noncompleters	16.6	5.7		
Psychological mindedness				
Completers	137.6	8.0	0.54	0.60
Noncompleters	135.1	10.1		
Previous therapies				
Completers	2.3	1.7	0.99	0.34
Noncompleters	3.1	1.6		
Education				
Completers	6.7	0.9	2.06	0.08
Noncompleters	5.0	2.0		

	SSRI	SNRI	Bupropion	χ^2	p
Medication use					
Completers	6	1	2	1.10	0.58
Noncompleters	3	2	2		

SD = Standard deviation; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor. Education was rated on a scale from 1 to 8 as follows: 1 = grade 6 or less; 2 = grade 7–12 without graduation; 3 = high school diploma or equivalent; 4 = some college; 5 = 2-year college degree; 6 = 4-year college degree; 7 = some graduate school; 8 = graduate degree.

We also contrasted pretreatment scans in patients who ultimately completed treatment versus those who terminated early; in regions showing significant between-group differences, rCMRglu was tested for correlation with Psychological Mindedness Scale scores.

Results

Pretreatment Characteristics and Completion

Among 35 patients who consented for participation, 12 failed to meet inclusion criteria and an additional 7 declined to participate in PET scans, leaving 16 who underwent pretreatment scans (table 2). Of these, 9 fully completed treatment and 7 discontinued early. All participants had multiple prior depressive episodes. Completers did not differ significantly from noncompleters on demographic or clinical measures.

Change in Depression and Therapeutic Alliance

Among completers, HamD-17 scores dropped by a mean of 67% at the conclusion of treatment (online suppl. fig. S1A), with 7 of 9 patients achieving ≥50% score reduction. Significant score reductions were evident at week 4, and scores remained significantly lower than before treatment at the 3-month follow-up. Noncompleters exhibited neither significant changes in HamD-17 scores from pretreatment, nor significant differences from completers.

Patient and therapist Working Alliance Inventory scores are plotted in online supplementary figure S1B. Among completers, alliance measures for patients and therapists closely overlapped, with both gradually increasing. Patient and therapist ratings for noncompleters also overlapped; however, starting at week 4, these scores were significantly lower compared to completers.

Psychotherapy Process

Online supplementary table S1 lists the PQS items that were rated as most characteristic of therapy sessions, averaged across participants. Several items indicate clear adherence to the CCRT manual (e.g. focus on self-image and interpersonal relationships), whereas others reflect the structured and time-limited nature of the intervention (e.g. therapist-structured interaction).

PET Correlates of Depression

Before treatment, a significant positive correlation between rCMRglu and HamD-17 scores was identified within a large cluster in the right posterior insula extending to two smaller clusters in the parietal cortex ($p < 0.05$, corrected for whole-brain volume; fig. 1a; online suppl. table S2). No significant clusters showed an inverse relationship between rCMRglu and depression scores. Within the right insula cluster, there was no significant change in absolute rCMRglu over time. However, percent change in rCMRglu correlated significantly with percent change in HamD-17 scores, where decline in insula rCMRglu predicted decline in depression scores ($\rho = 0.67$; $p = 0.05$; online suppl. fig. S2A).

Planned post hoc correlations of right insular rCMRglu percent change with the average scores for each PQS item revealed significant association with only one PQS item after correction for multiple comparisons:

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Fig. 1. a Correlation between brain glucose metabolism before treatment and depression scores (n = 16). The image represents a statistical parametric map, thresholded at voxel-wise p < 0.001 and whole-brain volume threshold for cluster-wise probability of α < 0.05, conferring correction for multiple comparisons. Three clusters within and adjacent to the right posterior insula demonstrated a significant, positive correlation between pretreatment HamD-17 score and rCMRglu. No significant clusters demonstrated an inverse correlation between these measures. Color bar indicates t score. L = Left; R = right. **b** Pretreatment differences in precuneus metabolism between completers (n = 9) and noncompleters (n = 7). Statistical parametric map compares glucose metabolism in completers versus noncompleters, thresholded at p < 0.001 and whole-brain volume threshold for cluster-wise probability of α < 0.05, conferring correction for multiple comparisons. Completers demonstrated significantly higher rCMRglu within the right precuneus compared to noncompleters. Color bar indicates t score. L = Left; R = right. **c** Across all participants, pretreatment metabolism within a spherical region-of-interest centered in the right precuneus correlated positively with psychological mindedness (ρ = 0.70; p = 0.002).
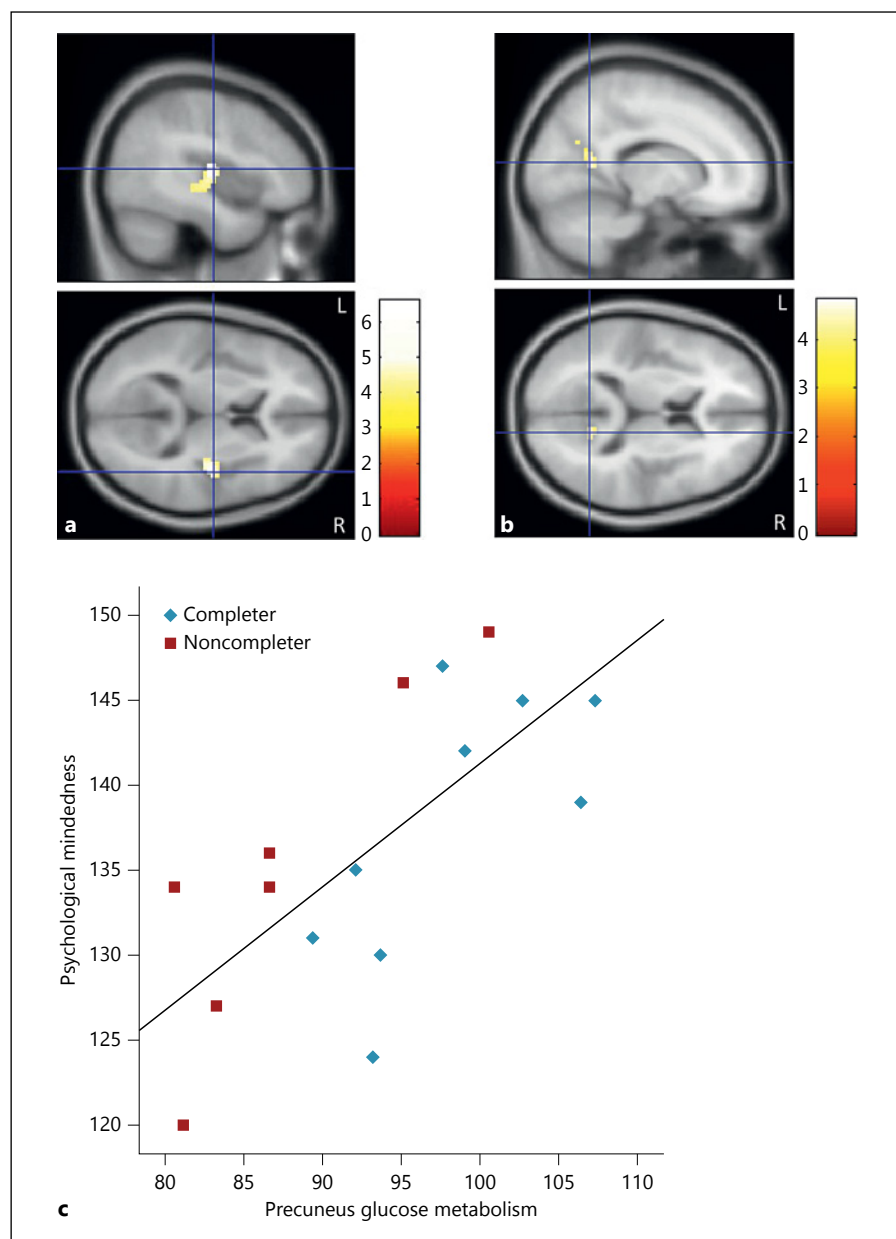
item 32, 'Patient achieves a new understanding or insight' (ρ = –0.92; p = 0.0004; online suppl. fig. S2B). Patients with greater reductions in insular metabolism were given higher insight ratings.

PET Predictors of Treatment Completion

Comparison of pretreatment PET scans for completers (n = 9) versus noncompleters (n = 7) identified a single cluster within the right precuneus, where completers exhibited greater rCMRglu (p < 0.05, corrected for whole-brain volume; fig. 1b; online suppl. table S3). Within the

right precuneus, rCMRglu was positively correlated with the Psychological Mindedness Scale score (fig. 1c). The inverse contrast of noncompleters versus completers failed to identify significant differences in pretreatment rCMRglu.

Discussion

To our knowledge, this is the first FDG-PET investigation to study neural correlates of psychodynamic psychotherapy in depression. Among patients who completed

treatment, improvement in depression scores correlated with reduced insula metabolism, which in turn was associated with a specific measure of the psychotherapy process – achievement of insight – that is highly characteristic of successful psychodynamic treatments [12]. Further, treatment completers exhibited higher pretreatment metabolism in the right precuneus than did noncompleters. Pretreatment precuneus metabolism was also associated with psychological mindedness, considered by many as critical to successful dynamic treatments. This convergence of findings provides evidence that brief psychodynamic psychotherapy both relies upon and modulates specific aspects of brain function.

The insula plays an essential role in self-monitoring and is frequently implicated in brain imaging studies of depression, mindfulness, interoception, and emotion regulation [13–16]. Insula findings in neuroimaging treatment studies of depression are common, yet have varied. Higher pretreatment insular metabolism was associated with greater antidepressant response to escitalopram than to cognitive behavioral therapy in one recent study [17], whereas other studies have shown increased posttreatment insular/limbic metabolism following cognitive behavioral [18] and interpersonal therapy [19]. Direct comparisons between previous studies and the present one are complicated by methodological differences (e.g. differences in modes of psychotherapy, treatment standardization/process measures, and concurrent medications). However, each of these findings points to the insula as critically and fluidly involved in metabolic processes underlying depression.

The precuneus, located in the posteromedial parietal lobe, is a cortical 'hub' region with dense anatomical and functional connectivity to other areas of association cortex [20]. Numerous previous neuroimaging studies have associated precuneus activation with self-awareness (e.g. autobiographical memory, first-person perspective taking, and the experience of agency) [21]. Consistent with these findings, pretreatment resting precuneus metabolism was correlated with psychological mindedness, i.e. an individual's capacity for introspection and personal insight. Psychological mindedness has been associated with better outcomes specifically in psychodynamic treatments [22], but as with most interview- or survey-based instruments, it has only modest predictive value [23]. Here, completers and noncompleters did not differ significantly on psychological mindedness before treatment, suggesting that precuneus metabolism, as a neural substrate of psychological mindedness, can more sensitively predict treatment response.

A unique strength of the present study was the use of standardized psychotherapy process measures, obtained through trained raters' observations of videotaped sessions. Absent from previous neuroimaging studies of psychotherapy [5], process measures can both index adherence and parse specific symptom changes. The subjective nature of psychotherapy, even under standardized or manualized conditions, complicates between-subject comparisons. Using the PQS, several investigators have found that psychotherapies that have been conceived as 'psychodynamic' actually rely primarily on cognitive behavioral processes [24, 25]. Here, we found that process measures that were most characteristic of videotaped sessions aligned well with the central tenets of the CCRT manual (e.g. a focus on recurrent interpersonal themes). We also observed that patients' achievement of insight, a critical goal of psychodynamic work, was tied to changes in insula metabolism. This pattern argues against insula metabolism as merely being a proxy for depression state or that insula changes reflected a nonspecific 'placebo'-type effect.

As with other recent work [17], the present findings could take a step forward in the use of neuroimaging to improve treatment selection in individuals with depression. A critical consideration in our selection of an imaging modality was its potential to be deployed in clinical settings, where ^{18}FDG-PET (which is used ubiquitously) has a clear advantage over functional magnetic resonance imaging (which is primarily a research tool). We included individuals who had already experienced an incomplete response to antidepressant treatment, a common occurrence. For these individuals, who have already invested time and resources in treatment, it becomes especially important to rapidly identify a treatment that is more likely to work. As in other studies of psychodynamic psychotherapy [3, 4], the rate of premature termination was substantial; clearly, this form of treatment does not benefit all patients equally. Herein, the first clinical indicators of treatment success, i.e. statistically significant improvement in depression scores and separation from noncompleters in therapeutic alliance measures, only became apparent after 4 weeks of therapy. However, pretreatment precuneus metabolism demonstrated utility in differentiating those patients who would go on to complete treatment from those who would terminate prematurely.

In addition to the small sample size, several additional limitations of this study are important to address. We did not include a comparison group, raising the possibility that depression and PET changes reflected nonspecific effects of treatment (placebo effect). As discussed above,

the fact that brain metabolism changes tracked specifically with a process measure that is central to psychodynamic therapy argues against this concern. Psychotherapy process ratings were limited to 2 sessions per subject and may not have been representative of the rest of the treatment; however, the strong correlation of scores between the 2 sessions ($\rho = 0.65$) suggests that the ratings were generalizable. Finally, our findings may not apply equally well for less experienced therapists or across other forms of psychodynamic treatment, although by their nature, open-ended treatments are more heterogeneous and therefore more difficult to study.

In summary, although preliminary and requiring replication, the present results demonstrate neural correlates of short-term psychodynamic psychotherapy for depression. They relate regional brain glucose metabolism to relevant clinical measures from the beginning and end of treatment, as well as to process measures obtained during the treatment. They also demonstrate promise for the use of brain imaging to improve the efficiency of psychotherapy treatment selection, a critical issue for individuals who have shown an incomplete response to antidepressant medications.

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