Review of Psychodynamic Psychotherapy Neuroimaging Studies
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Corresponding author:
Allan A. Abbass (MD FRCPC) [1] allan.abbass@dal.ca
8203 5909 Veterans Memorial Lane
Halifax, NS, Canada, B3H 2E2
Telephone: 902-473-2514
Fax: 902-473-4545

Co-authors:
Sarah J. Nowoweiski (DPsych), [2] sarah@bluexpress.com.au
Denise Bernier (PhD), [1] dcbernie@dal.ca
Robert Tarzwell (MD, FRCPC), [3] rtarzwell@gmail.com
Manfred E. Beutel (MD), [4] Manfred.Beutel@unimedizin-mainz.de

[1] Department of Psychiatry, Dalhousie University; Centre for Emotions and Health, Halifax, Nova Scotia, Canada
[2] Melbourne Centre for ISTDP, Melbourne, Australia
[3] Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[4] Clinic for Psychosomatic Medicine and Psychotherapy, University Medicine, Mainz, Germany

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Abstract

Background: The clinical efficacy of psychodynamic psychotherapy has undergone extensive study and review. Recently, researchers have studied the effects of this treatment on brain metabolic or synaptic activity, but the collective findings have never been reviewed. The objective of this review was to describe the findings of all neuroimaging studies of any form of psychodynamic psychotherapy treatment.

Methods: An extensive literature search through databases along with surveying of research groups were undertaken to acquire all available published studies.

Results: Eleven series were included in the final sample, consisting of two randomized controlled trials, five controlled trials and four case series, altogether involving 210 people (116 with mental illness and 94 healthy controls) with mood disorders, panic disorder, somatoform disorders and borderline personality disorder. A variety of neuroimaging techniques were used to examine regional metabolic activity and synaptic neurotransmission before and after treatment. The common finding was normalization of synaptic or metabolic activity in limbic, midbrain and prefrontal regions, occurring in association with improved clinical outcomes.

Conclusion: Psychodynamic psychotherapy has demonstrable effects on brain function in diverse clinical populations as evidenced by a modest group of mixed neuroimaging studies.

Introduction

Psychodynamic psychotherapy (PDT) has recently undergone extensive study, meta-analysis and review [1]. The clinical benefits of this therapeutic approach are now supported by meta-analyses of randomized controlled trials across mood [1], somatoform [2], personality [3], and mixed disorders [4]. The outcome literature, therefore, demonstrates an empirical foundation for the clinical efficacy of PDT. However, neuroimaging exploration of the brain substrates of these effects has only recently begun.

Reviews of the neuroimaging markers of effects of psychotherapeutic modalities, including cognitive behavioral therapy (CBT) and interpersonal therapy (IPT), have recently been published. In general such reviews have documented normalization of baseline abnormalities, defined as no significant differences compared with expected norms or with non-psychiatric comparison subjects on the relevant measure, after successful psychotherapy. Further, neuroimaging changes were associated with symptom reduction [5-9]. These studies have implicated specific brain regions involving affect-regulatory systems (amygdala, insula, orbital prefrontal cortex, and subgenual cingulate cortex), memory (hippocampus) and procedural memory (basal ganglia) systems, as well as attentional and conscious self-reflective systems (dorsal prefrontal regions) [10].

A systematic review of neuroimaging studies of anxiety and depressive disorders compared the changes in cerebral metabolic activity after successful treatments with selective serotonin reuptake inhibitors (SSRIs; 33 studies) or with CBT (30 studies) [5]. Both treatment approaches normalized metabolic activity in brain regions typically implicated in these disorders. However, pharmacological treatments mainly tended to reduce baseline overactivity in ventral prefrontal and limbic structures, while CBT mainly tended to increase baseline hypoactivity in dorsal prefrontal regions.

Another comprehensive review focused on the neurobiological effects of different psychotherapy approaches with major depressive disorder (MDD) [6]. After successful CBT (7 studies), IPT (3 studies) and PDT (1 study) normalization of metabolic activity was detected in several brain regions including amygdala as well as prefrontal and cingulate cortices.

In this study, we reviewed neuroimaging studies involving PDT. This psychotherapy focuses on identifying and addressing unconscious feelings, impulses and conflicts that result in a broad range of symptoms and personality problems. By recognizing these processes and working through the emotions, patients can theoretically be freed from the effects of the past, become able to form healthy relationships, and experience a marked reduction in symptoms [1]. We hypothesized that PDT would have brain effects that parallel clinical improvement.

Methods

Methods and results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11].

Selection (Inclusion Criteria)

We compiled all available neuroimaging studies reporting on baseline and post-treatment measures after PDT treatment in non-brain damaged adults, and published in English or with English abstracts until August 2013.

Search Procedures

An electronic search was performed using PubMed Medline, PsycInfo, and Web of Science databases with the following key words: ‘psychodynamic’, ‘psychoanalytic’, ‘psychotherapy’, ‘treatment’, ‘therapy’, ‘neuroimaging’, ‘PET’, ‘SPECT’, ‘SPET’, ‘fMRI’,

'functional neuroimaging', and 'brain imaging'. A request was also sent to a membership-based forum of psychotherapy researchers for articles on this topic including In Press articles. Reference lists of articles were explored for further relevant articles.

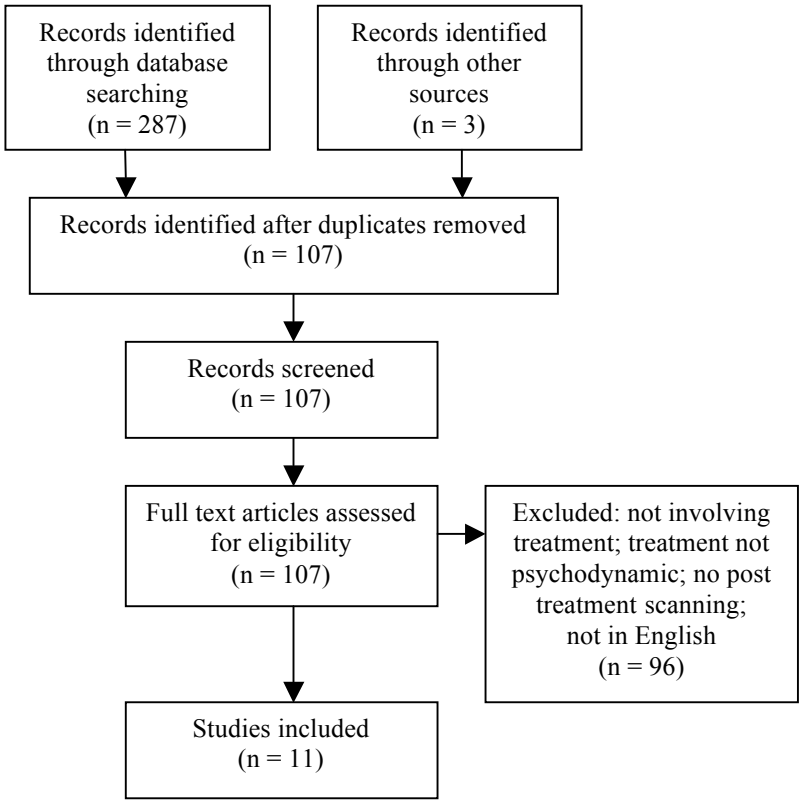
Data Collection and Assessment of Methodological Quality

Consensus agreement that a paper met inclusion criteria was required between two authors in order to finally include it in this review. Data were extracted and interpreted by two authors, and all authors reviewed the articles as a crosscheck on accuracy of interpretation of the data.

Results

Description of Studies

The search identified 107 articles in total after removing duplications and articles of the same series. Of these, 96 series were excluded because they involved no treatment, or the treatment was not psychodynamic, or the language was different from English. Eleven series were included in the final selection involving a total of 210 people (116 with mental illness and 94 healthy controls) and a range of psychiatric illnesses including depression (atypical and typical), mixed depression, borderline personality disorder, panic disorder and somatoform disorder. The series consisted of two randomized controlled trials [12, 13], five controlled trials [14, 15] and four case series [16-19]. The search is illustrated in Figure 1 (supplementary materials).



Treatment interventions were classified as PDT when defined by a manualized treatment protocol with established efficacy or by clear criteria outlined in the methodology, involving interventions focusing on unconscious conflicts as they emerge in the therapeutic or transference relationship. The number of psychotherapists providing treatment interventions varied from 1 to 16 for series conducted in outpatient settings and was unspecified in the two

series conducted in inpatient settings. Five series described the formal training and experience of the therapists [12-14, 17, 18].

Treatment settings included outpatient clinics for eight series, with individual psychotherapy sessions occurring either once a week [12, 13, 16, 19, 20] or multiple times per week [14, 17, 18]. These treatments involved from 16 to 120 hours of PDT treatment spread over 4 to 16 months. The other three series were conducted in inpatient settings [15, 21, 22] where mixed interventions along with individual psychodynamic therapy were employed over a period of 35 to 80 days.

The neuroimaging methods used in these series included single photon emission computed tomography (SPECT, sometimes abbreviated SPET), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [23].

At post-treatment, all included series reported group improvement from baseline clinical symptoms. Normalization of baseline scores was achieved in eight series [12, 13, 15, 16, 18, 20-22]. In one series [17], some features of borderline personality disorder remained after treatment but the participants no longer met diagnostic criteria. In another series [14], group baseline scores significantly improved with treatment but 5 of 16 participants still fulfilled diagnostic criteria for major depressive disorder at treatment endpoint.

Post-Treatment Neuroimaging Changes Relative to Baseline

The five functional neuroimaging series reported improvement in regional brain activation levels in response to emotionally or motivationally significant stimuli after PDT (Table 1, supplementary materials). In one series [15], post-treatment patients with panic disorder responding to emotionally valenced words showed no difference compared to controls: increased metabolic activity was observed in the ventral and orbital prefrontal regions, along with decreased activity in temporal regions. In a second series [14], post-treatment patients with depression had metabolic activity similar to controls in regions of amygdala, hippocampus and dorsal prefrontal cortex in response to attachment-related stimuli: treated cases had less activation than controls in the subgenual cingulate cortex. In a third and fourth series [21, 22], patients with somatoform disorders showed significant enhancement toward normalization and relative to controls in differential blood flow between anticipation of reward versus anticipation of no reward in regions of postcentral gyrus, dorsal anterior cingulate, occipital cortex, and ventroposterior thalamus. When presented with empathy paradigms versus control paradigms, patients showed significant enhancement toward normalization of brain activity with the emotion of anger in regions of parahippocampul gyrus, amygdala, superior temporal gyrus, posterior insula and postcentral gyrus. Finally, two patients with borderline personality disorder responded to a psychological stress condition at post-treatment time with levels of regional metabolic activity in frontal and limbic areas similar to the pre-treatment quiet condition, indicating lower levels of perceived stress; moreover, increased perfusion in frontal areas in response to stress following treatment was associated with improved impulse control [16].

Table . Findings from neuroimaging studies that used activation paradigms to study the effects of psychodynamic psychotherapy

First author (year) [ref]	Clinical condition (n)	Neuroimaging method and activation paradigm	Baseline differences relative to healthy controls	Post-treatment changes relative to baseline
Buchheim (2012) [14]	Depression (16) HC (17)	fMRI (metabolic activity) Emotional stimuli: attachment-related scenes	Patients showed overactivation in regions of amygdala/hippocampus, dorsal prefrontal areas, and ventral cingulate region (BA 25)	Patients showed a) reduced activation towards normalization in same regions b) less activation than controls in subgenual cingulate
Beutel (2010) [15]	Panic Disorder (9) HC (18)	fMRI Emotional paradigm: words with negative, neutral	Patients showed a) increased limbic activity to words with negative valence b) decreased ventrolateral PFC activity to words with	Patients displayed no difference from controls in these regions
de Greck (2011) [21]	Somatoform Disorder (15) HC (20)	fMRI Cognitive reward paradigms: anticipation of reward versus anticipation of no reward	Controls had increased activity with anticipation of reward in bilateral ventral striatum, frontal cingulate cortex, thalamus, and left posterior midbrain Patients showed no differentiation in metabolic activity between paradigms	Patients showed enhancement in neuronal differentiation (toward normalization) between paradigms
de Greck (2013) [22]	Somatoform Disorder (15) HC (15)	fMRI Emotional empathy paradigm: emotional face stimuli versus control stimuli	Patients showed less activity than controls during the empathy paradigm with the emotions of anger and joy relative to the control paradigm in several regions	Patients showed normalization of brain activity in almost all regions affected at baseline during empathy
Lai (2007) [16]	Borderline Personality Disorder (2) HC (5)	SPET (regional perfusion rates) a) baseline: quiet and stress conditions b) post-treatment: stress condition	Quiet condition: a) Patients showed hyperperfusion rates in frontal and limbic areas Stress condition (5 min duration video stimulus with psychologically violent scenes): a) Patients showed hyperperfusion rates in limbic, temporal, parietal and occipital areas b) HC had no changes in brain perfusion rates	Stress condition: Patients' perfusion rates were now similar to baseline quiet condition (indicating lower perceived psychological stress)

Table. Findings from neuroimaging studies of synaptic neurotransmission before and after psychodynamic psychotherapy

First author (year) [ref]	Clinical condition (n)	Neuroimaging (measure)	Baseline differences relative to healthy controls	Post-treatment changes relative to baseline
Hirvonen (2011) [12]	Depression: - treated with PDT (8) - or with Fluoxetine (14) No HC	PET (D2/3 binding)	N/A	PDT Group: No changes in dopamine D2/3 receptor binding availability in striatum and thalamus. Fluoxetine Group: Increased D2/3 binding potential in lateral thalamus but no changes in striatum
Karlsson (2010) [20] Karlsson (2013) [24]	Depression: - treated with PDT (8) - or with Fluoxetine (15) HC (4)	PET (5-HT_{1A} receptor binding potential)	Not provided	PDT group: Increase in 5-HT_{1A} binding after PDT with an effect size of 0.85 across brain regions: a) the prefrontal cortex: dorsolateral, medial, ventrolateral, orbital, and ventral anterior cingular; b) the insular cortex; c) the inferior and superior temporal gyri; and d) the parietal lobe: supramarginal and angular gyri. The increase in 5-HT_{1A} binding very strongly correlated with improvement in social functioning. Fluoxetine group: No changes in 5-HT_{1A} binding (and changes no greater than controls) Healthy controls: No changes
Lehto (2008) [13]	Atypical depression (8) Typical depression (11) No HC	SPECT (SERT & DAT)	No baseline difference in striatal DAT and midbrain SERT between the two clinical groups	Midbrain SERT increased in the group with atypical depression while no change was observed in people with typical depression
Saarinen (2005) [17]	Depression (1) HC (10)	SPECT (SERT)	Patient had decreased midbrain SERT (by -2.5 SD)	Patient midbrain SERT normalized
Tolmunen (2004) [18]	Hypomania and dysthymia (Case1) Depression (6) HC (10)	SPECT (SERT & DAT)	Case 1: Elevated midbrain SERT (+2 SD); elevated striatal DAT. Patients with depression: decreased midbrain SERT	Case 1: decreased midbrain SERT and striatal DAT (towards normalization) Depressed group showed increased SERT availability (towards normalization)
Viinamaki (1998) [19]	Borderline personality disorder with -Case 1: mild depression -Case 2: severe depression HC (10)	SPECT (SERT & DAT)	Case 1: decreased SERT (by 2 SD) in medial prefrontal cortex, midbrain, thalamus; normal striatal DAT	Case 1: SERT increased (normalized) in medial prefrontal region, midbrain and thalamus; no changes Case 2: no changes (and did not complete treatment)

Synaptic Neurotransmitter Studies

The six series of synaptic neurotransmission reported improvements toward normalization in neuroimaging measures after PDT (Table 1, Table 2 supplementary materials). Increased midbrain serotonin transporter binding (SERT) toward normalization or control values was observed in an aggregate total of 16 patients with either atypical depression [13], severe to moderate depression [17, 18], or borderline personality disorder with mild depression [19]. Increased SERT was also found in the medial prefrontal cortex of one patient with depression and in the medial prefrontal cortex and thalamus of one patient with borderline personality disorder with mild depression [19]. On the other hand, a single case of dysthymia and hypomania [18] showed a decrease (normalization) in midbrain SERT after treatment. In regards to dopamine transporter binding (DAT) densities, normal baseline and post-treatment levels were found in the striatum of patients with atypical or typical depression [13] and in the limbic structures of patients with depression [13, 19]. However, striatal DAT densities decreased toward normalization for the case with depression and hypomania [18]. In one PET series, D2/3 receptor binding assessed in patients with depression remained stable in the thalamus and striatum after PDT treatment, while it increased with antidepressant medication (Fluoxetine) in the lateral thalamus [12]. In a separate series of the same sample, $5HT_{1A}$ receptor binding potential increased significantly in a depression group after treatment with PDT, with an effect size of 0.85 across brain regions; the brain regions involved the dorsal, subgenual and subcallosal anterior cingulate gyrus and mid-temporal region [20]. This increase in $5HT_{1A}$ receptor binding was not seen in patients treated with fluoxetine, despite similar clinical improvement in both clinical groups. In patients who had reached remission (HAM-D $\leq$ 7) after PDT (n = 4), post-treatment increase in $5HT_{1A}$ receptor binding strongly correlated with improvement in HAM-D depression ratings. Treatment with fluoxetine brought no significant changes in $5HT_{1A}$ receptor binding in this group, and no more changes than observed in controls [20]. In a later analysis, Karlsson and colleagues found that this increase in $5HT_{1a}$ receptor binding correlated with improvement in social adjustment in the PDT group, but, not in the fluoxetine group [24].

Table . Direction of differences in synaptic neurotransmission after psychodynamic psychotherapy

Brain region	Clinical condition	Baseline (N across studies)	[ref]	Post-treatment (N across studies)	[ref]
Midbrain	Depression	↓ SERT (9)	[20-22]	↑ SERT (16)	[13,20-22]
	Hypomania	↑ SERT (1)	[21]	↓ SERT (1)	[21]
Thalamus	Depression	↓ SERT (1)	[22]	↑ SERT (1)	[22]
	Depression			= D2/3 binding (8)	[12]
	Depression			↓ D2/3 binding (14) (after Fluoxetine)	[12]
Medial prefrontal	Depression	↓ SERT (2)	[22]	↑ SERT (2)	[22]
Subgenual/subcallosal prefrontal	Depression			↑ $5HT_{1A}$ (8)	[17]
Mid-temporal	Depression			↑ $5HT_{1A}$ (8)	[17]
Striatum	Depression	= DAT (8)	[21,22]	= DAT (21)	[13,22]
	Depression			= D2/3 binding (8)	[12]
	Hypomania	↑ DAT (1)	[21]	↓ DAT (1)	[21]

DAT, dopamine transporter binding. SERT, serotonin transporter binding. $5HT_{1A}$, serotonin receptor binding.

Discussion

This review compiled findings from a series of diverse neuroimaging series showing brain functional and neurochemical changes in response to psychodynamic psychotherapy. In the four disorders studied, patterns of neural activity or neurophysiological infrastructure in regions of dorsolateral prefrontal cortex (DLPFC), orbital frontal cortex (OFC), anterior cingulate cortex (ACC) and amygdala differed between clinical cases and healthy controls prior to treatment, while after treatment, the patterns seen in patients resembled those of controls. As the post-treatment changes in baseline measures of brain function correlated with improvement in clinical presentation, these neurobiological changes appear indicative of improvement on a biological level [12-19, 21, 22]. Such improvements in neuroimaging measures might reflect neural correlates of the changes effected by PDT and expressed clinically as symptom reduction [1-4].

It is notable that activity levels in brain circuits that appear to be involved in processes of interest to psychodynamic theory appear aberrant in pathological states and show improvement after a course of PDT. While much remains to be understood about what these patterns of activity revealed by neuroimaging mean on a functional level [25], it is possible to speculate about some of the findings summarized in this review. For example, baseline overactivity in regions associated with emotion may relate to activated but unprocessed emotions that are brought to consciousness during PDT [14, 15, 21, 22]. In depression, post-treatment reduction of regional activity in the subgenual ACC, an area associated with guilt [26], self-defeat [27] and repression of emotions [28] may reflect overcoming of repression of emotions and reduction in unconscious guilt, thus, resulting in a better relationship with oneself, and, antidepressant effects [14]. In borderline personality disorder cases, improvement in DLPFC function may reflect a transition to more mature defenses with PDT [16]. Such findings warrant replication and a priori hypothesis testing to examine the neuroimaging changes observed when specific PDT processes take place.

With the advent of neuroimaging studies of different psychotherapy models such as PDT and CBT, researchers may generate testable hypotheses about which baseline neuroimaging markers relate to treatment response when these different models are used [29]. For example, Buccheim and colleague's finding that PDT was effective in depression cases with subgenual ACC overactivity where others have found CBT [30] and CT [31] do not appear to be effective in such cases, is of interest and may warrant formal study. Such efforts to use imaging data to predict treatment outcomes is in its early stages and requires standardization of methodologies before robust baseline treatment predictors can be identified [29].

In the same vein, one can now use neuroimaging to study the effects of treatment ingredients common to different therapy models, such as levels of adherence, therapeutic alliance or emotion activation [32, 33]. Combined, such neuroimaging research may help clarify the relationships of treatment variables to both short and long-term outcomes toward elucidating what works for whom.

This review has a number of limitations rendering its findings preliminary. First, the numbers of series and included patients were small. Second, not all series included healthy subjects to control for effects of time and repeated testing. Third, there was variation in imaging methodologies between series. Fourth, the reviewed sample included diverse populations and diagnostic categories. Fifth, a mix of psychodynamic therapeutic models may have been used in these series, and the frequency of sessions and duration of treatment were variable across series. Finally, although most PDT treatments were the sole treatment provided in an outpatient setting, other series were part of integrated treatment efforts on inpatient settings; hence, other factors may have accounted for the observed changes. Therefore, the findings of these studies are currently insufficient to build any models of consistent changes in brain structure and function associated with psychodynamic treatment, but, the summary of the these findings provided above may serve as a foundation for further exploration.

In conclusion, there is preliminary data that PDT correlates with specific neurobiological changes in diverse populations. Further research is indicated to study brain changes both within PDT [31] and between psychotherapy models in order to help identify specific therapeutic ingredients operating within specific populations.

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Authors' potential conflict of interest:
The authors use psychodynamically-oriented psychotherapy with a variety of clinical populations.

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