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Psychotherapy and neuroscience: Towards closer integration

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Psychotherapy and neuroscience: Towards closer integration

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The original aim of psychology was to study and understand the spirit—from the Latin *spiritus*, literally “breath.” The limitations of scientific methods in the past favoured psychology’s aloofness in terms of studying the “intangible,” while medicine developed methods of examining the body (Latin *corpus*: essential part). Until 20 years ago, knowledge of the localization of brain functions was limited to inferences from clinical observation of brain-lesioned patients or parallel studies of primate brains. Current neuroscience, with its integrative approach, is bringing together research from molecular through cognitive levels, and psychotherapy has benefited from these findings. Functional neuroimaging studies may make specific and more far-reaching contributions in this respect, since cerebral dynamics may be observed *in vivo* and in controlled situations. Methods such as single photon emission tomography, positron emission tomography, and functional magnetic resonance imaging have been able to evaluate the neural correlates involved in psychotherapy for individuals with obsessive-compulsive disorder, major depression, social phobia, specific phobia, and post-traumatic disorder. Researchers have found that psychotherapy has the potential to modify dysfunctional neural circuits associated with these disorders. However, precautions are required in constructing feasible designs for neurofunctional investigations. This article reviews the 21 studies that have been published on the subject, and sets out the main advantages and limitations of the technologies used most frequently in protocols involving psychotherapies, and prerequisites for experimental designs. We also pose ways in which the findings from neuroimaging may produce knowledge to guide psychotherapeutic interventions by specifying what should be stimulated in these individuals in order to normalize deficient neural activities.

À l’origine, le but de la psychologie était d’étudier et de comprendre l’esprit—du latin *spiritus*, littéralement « souffle ». Les limites des méthodes scientifiques, dans le passé, ont amené la psychologie à exercer une réserve quant à l’étude de l’« intangible », tandis que la médecine a développé des méthodes permettant d’examiner le corps (latin *corpus* : partie essentielle). Jusqu’à il y a 20 ans, les connaissances sur la localisation des fonctions du cerveau étaient limitées aux inférences à partir d’observations cliniques des patients ayant subi des lésions cérébrales ou aux études parallèles menées sur les cerveaux de primates. La neuroscience actuelle, avec son approche intégrative, permet de rassembler la recherche moléculaire à travers les niveaux cognitifs et la psychothérapie, laquelle a bénéficié de ces données de recherche. Les études de neuro-imagerie fonctionnelle peuvent apporter des contributions spécifiques et d’une portée considérable depuis que les dynamiques cérébrales peuvent être observées *in vivo* et en contrôlant les situations. Des méthodes aussi simples que la tomographie d’émission de photons, la tomographie d’émission de positrons et l’imagerie par résonance magnétique fonctionnelle ont aussi été capables d’évaluer les composantes neuronales impliquées en psychothérapie pour les individus ayant un trouble obsessionnel-compulsif, une dépression majeure, une phobie sociale, une phobie spécifique et un trouble post-traumatique. Les chercheurs ont trouvé que la psychothérapie avait le potentiel de modifier les circuits neuronaux dysfonctionnels associés avec ces troubles. Cependant, des précautions sont requises dans l’élaboration de designs possibles pour des études neurofonctionnelles. Cet article présente les 21 études qui ont été publiées sur le sujet. Il fait ressortir les principaux avantages et limites des technologies utilisées le plus fréquemment dans les protocoles impliquant des psychothérapies, ainsi que les conditions nécessaires pour les designs expérimentaux. Nous abordons également comment les résultats de neuro-imagerie peuvent accroître les connaissances pour guider les interventions psychothérapeutiques, en spécifiant ce qui doit être stimulé chez les

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individus pour normaliser leurs activités neuronales déficientes.

*E*l propósito original de la Psicología fué el estudio y la comprensión del espíritu—del latín *spiritus*, traducción literal, “aliento”. Las limitaciones de los métodos científicos en el pasado favorecieron el aletargamiento de la psicología en términos del estudio de lo “intangible”, en tanto la medicina desarrolló métodos para examinar el cuerpo (del latín *corpus*: parte esencial). Hasta hace veinte años el conocimiento sobre la localización de las funciones cerebrales estaba limitado a inferencias de la observación clínica en pacientes con lesiones cerebrales o en estudios paralelos con cerebros de primates. En la actualidad la Neurociencia con su aproximación integradora está investigando de manera conjunta desde el aspecto molecular hasta los niveles cognitivos, y la psicoterapia se ha beneficiado de esos hallazgos. Estudios con técnicas de neuroimagen funcional están haciendo contribuciones específicas y más provechosas a este respecto, desde que los dinamismos del funcionamiento cerebral pueden ser observadas en vivo y en situaciones controladas. Métodos tales como la tomografía por emisión de fotón único (SPECT), la tomografía por emisión de positrones (PET) y la imagen funcional por resonancia magnética (fMRI) se han mostrado capaces de evaluar los correlatos neuronales comprometidos en la psicoterapia de personas con un transtorno obsesivo-compulsivo, depresión mayor, fobia social, fobia específica y desorden posttraumático. Los investigadores han encontrado que la Psicoterapia tiene el potencial de modificar circuitos neuronales disfuncionales asociados con estos desórdenes. Naturalmente, se requiere determinadas precauciones en el diseño de investigaciones neurofuncionales confiables. El presente artículo revisa los veintidós estudios que han sido publicados en este campo y precisa las principales ventajas y limitaciones de las tecnologías usadas con mayor frecuencia en protocolos que incluyen psicoterapias, así como los pre-requisitos para el diseño de investigaciones. Adicionalmente, proponemos algunas vías a través de las cuales los hallazgos logrados con técnicas de neuroimagen puedan generar conocimiento que guíe las intervenciones psicoterapéuticas, especificando los aspectos a ser estimulados en esas personas con el fin de normalizar la actividad neuronal deficiente.

The idea of brain functions being related to anatomical instantiations was no more than a hypothesis in the mid-19th century, but started to acquire substance after controlled experiments such as those conducted by Broca (1861), Jackson (1931), and Penfield (1952). In this period, most human brain-related data came from observing brain-lesioned individuals affected by loss of function or impaired behaviours. Given the limitations of this type of knowledge, the removal of certain parts of the brain was used as treatment strategy for individuals with neurological disorders (Sperry, 1968). Until 20 years ago, knowledge of the localization of encephalic functions was limited to inferences from clinical observation of brain-lesioned patients or parallel studies of primate brains (Kandel, Schwartz, & Jessell, 2000, p. 366). The development of methods for investigating the human brain in vivo then led to an emphasis on specialization associated with new technology as generations of researchers narrowed their focus to ever more specific sectors (Finger, 1994). Due to this historical trend, there has been a persistent tendency to divide psychiatric or psychological disorders into “brain” and “mind” diseases, with the corollary of dichotomized and often mistaken therapeutic behaviours: “If diseases are ‘mental,’ the mind should be treated with psychotherapy; but if they are physical or ‘cerebral,’ physical treatments affecting the brain should be used, such

as medications” (Andreasen, 2004, p. 34). Recent and current neuroscience findings show that cognitive, emotional, perceptual, and behavioural functions are mediated by specific areas and circuits of the brain, and that the nonintegrity of certain neural systems may more easily be associated with disorders of the respective functions (Epstein, Stern, & Silbersweig, 2001). However, the brain’s plasticity, being directly related to learning and memory, may modify, offset, generate, or adjust neural functions that are crucial to adaptive life (Squire & Kandel, 2003, p. 54). A new generation of mental health professionals is gradually correcting the biased dichotomy on the basis of neuroscience, showing that the mind/cognition may override the brain and modify its functional dynamics through learning (Paquette et al., 2003; Rainville, Hofbauer, Bushnell, Duncan, & Price, 2002; Rybakowski, 2002). Functional neuroimaging technologies (see Table 1) are perhaps the most important of several recent developments that promise to correct, or even eliminate, the rigid classification of disorders as neurological, psychiatric, or psychological. In fact, neuroscience and its integrative approach is bringing together research on different levels, from the molecular to the cognitive, and pointing to relations of dynamic interdependence between functions at these levels (Finger, 1994; Kandel et al., 2000, p. 4).

TABLE 1
Advantages and limitations of neuroimaging technologies

<i>Technology</i>	<i>Spatial resolution</i>	<i>Temporal resolution</i>	<i>Advantages</i>	<i>Limitations</i>
SPECT	8–15 mm	3–5 minutes	<ul style="list-style-type: none"> · Acquisition of images after injecting tracer (reduces artifacts of motion) · Allows use of familiar setting for subject (e.g., a therapeutic setting) · Uses more stable tracers with longer half-life (4 to 6 hours) · Costs are lower and the method is more readily available 	<ul style="list-style-type: none"> · Invasive (requires injection of radioisotope marker) · Experiments cannot be repeated within a short period · Limited resolution, does not acquire anatomy · Nondynamic examination (measures one continuous task over a single period) so is restricted to studies involving nonvarying tasks
PET	4.5–15 mm	seconds / minutes	<ul style="list-style-type: none"> · Temporal dynamics (measuring variations in the course of the task) · Provides good spatial localization in active areas · Use of different tracers for metabolic studies with neuromediators 	<ul style="list-style-type: none"> · Invasive (radioisotope marker has to be injected) · Experiments cannot be repeated frequently in a short period of time · Subjects must remain immobile (prone to artifacts of motion) · Tracers are unstable, with short half-life (minutes).
fMRI	1–3 mm or higher	30 ms–1 s	<ul style="list-style-type: none"> · High spatial and temporal resolution · Enables researchers to correlate neural activity with underlying anatomy · Noninvasive (no radiation) · Several paradigms may be used with a simple examination and several trials in a short period 	<ul style="list-style-type: none"> · Measures haemodynamic response rather than neural activity itself · Signal intensity is variable, even with constant stimulus intensity · There may be false positives (BOLD effect occurs in excitatory and inhibitory synaptic activity) · There is EPI noise (averaging 80 dB) during acquisition · Persons with magnetic implants or materials have to be excluded

SPECT: single photon emission computed tomography; PET: positron emission tomography; fMRI: functional magnetic resonance imaging.

Our aim in this article is to show how the bond between psychotherapy and neuroscience is being strengthened by the use of functional neuroimaging. The technologies most often used in protocols involving psychotherapies will be introduced, and we shall address the precautions required in constructing feasible designs for neurofunctional investigations. Finally, we shall look at signs of this integrative neuroscience era that has now begun and discuss how to cultivate the healthy approach of analysing and producing science for the benefit of individuals seeking psychotherapy.

PSYCHOTHERAPY: FROM CRADLE TO MATURITY

The roots of psychology go back to Ancient Greece and Aristotle (384–322 BC), whose *On the Soul* is often viewed as the first handbook of

psychology (Aristotle, 1956). However, the term “psychology” itself emerged only in the late 16th century, with Rodolfo Goclenio’s *Psychologia, hoc est de hominis perfectione, animo et in primis ortu eius, commentationes ad disputationes*, its etymological roots being *psyche* (soul) and the suffix *logos* (reason, study). The original aim of psychology was to study and understand the spirit—from the Latin *spiritus*, literally “breath.” The limitations of scientific methods in the past favoured psychology’s aloofness in terms of studying the “intangible,” while medicine developed methods of examining the body (Latin *corpus*: essential part). As an example of this dichotomy, note that Freud only abandoned his work on these lines and narrowed his focus to the mental arena after concluding that using these methods would not enable him to translate clinical observations of mental processes into neurological terms (Kandel, 1998). Today, the neurobiological effects of

psychotherapy may be measured using functional imaging, which is now seen as extremely relevant for neuroscience and psychology, since we may gradually achieve more precise identification of the neural circuits associated with the disorders being studied. Studies involving neuroimaging and psychotherapy have brought together approaches from behavioural therapy, cognitive behavioural therapy, interpersonal therapy, eye movement desensitization, and reprocessing used mainly to treat obsessive-compulsive disorder, major depressive disorder, social/specific phobia, and post-traumatic stress disorder (Tables 2, 3, and 4).

THE PSYCHOTHERAPEUTIC EXPERIENCE AND THE NERVOUS SYSTEM

In the West, psychotherapies emerged in the mid-19th century under the influence of a number of different philosophical schools, epistemological perspectives, theories, and methods; their aim was to treat, remove, or modify symptoms of an emotional nature and foster development and personality growth. Several behaviours involve volition, so there may be a modulated relationship

between consciousness and the central nervous system (CNS) during these processes (McGaugh, Cahill, & Roozendaal, 1996; Poldrack & Packard, 2003). Neuroscience has shown that behaviour may be learned and improved through experience, which alters the “voltage” of neural network synapses to prompt formation of new neural circuits and new memories that will subsequently be accessible (Kandel et al., 2000, p. 34). Not only objective but subjective experiences, too, can alter the flow of neural information. Studies involving neuroimaging and visualization of specific physical exercises, such as pedalling a bicycle up an increasingly steep grade (I), pedalling steadily on the same level (II), and cycling steeply downhill (III), have shown important neurophysiological correlates. The insula and thalamus were activated with corresponding rises in cardiovascular response during induced and increasing physical effort (condition I) (Williamson et al., 2001). Another study showed that an imaginary auditory and visual situation obeyed neural correlates similar to those in the real-life state of hearing and seeing the same events (Kraemer, Macrae, Green, & Kelley, 2005). Primate studies have

TABLE 2
SPECT studies involving psychotherapy

<i>Study</i>	<i>Therapy type interval</i>	<i>Subjects</i>	<i>Control</i>	<i>Paradigm</i>	<i>Post-treatment decreases (↓) and increases (↑)</i>
Laatsch et al. (1999)	Cognitive rehab therapy, 6–36 sessions	5 patients with traumatic brain injury	None	Resting	↑ Global increases during treatment phase in 3 of 5 patients
Levin et al. (1999)	EMDR, 3 sessions	1 patient with PTSD	None	While being read scripts	↑ ACC and L frontal lobe
Martin et al. (2001)	IPT, 6 weeks	13 patients with MDD	15 patients with MDD given venlafaxine	Resting	↑ R basal ganglia and R PCC in IPT ↑ R basal ganglia and posterior temporal cortex (venlafaxine)
Penades et al. (2002)	Group neuropsychological rehab, 12 weeks	8 patients with schizophrenia, on olanzapine	None	During Tower of London task	↑ frontal lobe, correlated with improvement in test score
Nakatani et al. (2003) with Xe-CT	BT, duration depending on clinical improvement	31 patients with treatment refractory OCD	31 healthy controls	Resting	↓ R caudate
Johanson et al. (2006) with Xe-CT	CBT, 3 months	6 patients with spider phobia	None	Resting and neutral / living spiders video recording	↑ PFC
Peres et al. (2006)	Cognitive Restructuring Therapy, 8 weeks	16 patients with partial PTSD	11 WL patients with partial PTSD	While being read personal scripts	↑ L hippocampus, parietal and L PFC ↓ amygdala

R: right; L: left; BT: behavioural therapy; CBT: cognitive behavioural therapy; IPT: interpersonal therapy; EMDR: eye movement desensitization and reprocessing; WL: waiting list; PTSD: post-traumatic stress disorder; Xe-CT: xenon-enhanced computed tomography; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; PFC: prefrontal cortex.

TABLE 3
PET studies involving psychotherapy

<i>Study</i>	<i>Therapy type interval</i>	<i>Subjects</i>	<i>Control</i>	<i>Paradigm</i>	<i>Post-treatment decreases (↓) and increases (↑)</i>
Baxter et al. (1992)	BT, 10 weeks	9 patients with OCD	9 patients with OCD, taking fluoxetine and 4 healthy subjects	Resting	↓ R caudate in both groups Correlation between R OFC, caudate and thalamus Cortico-striato-thalamic circuit in combined subject pool
Schwartz et al. (1996)	CBT, 10 weeks	9 patients with OCD, plus earlier cohort	None	Resting	↓ caudate bilaterally Correlation between R OFC, caudate and thalamus Uncoupling of cortico-striato-thalamic circuit
Brody et al. (1998)	BT, 8–12 weeks	18 patients with OCD	9 patients with OCD given fluoxetine	Resting (at baseline only)	↑ L orbitofrontal correlated with treatment response
Brody et al. (2001a)	IPT, 12 weeks	14 patients with MDD	10 patients with MDD given paroxetine	Resting	↓ bilateral PFC, L ventral ACC and ↑ L temporal cortex and insula in IPT ↓ bilateral PFC, L middle ACC and ↑ L temporal cortex and insula (paroxetine)
Brody et al. (2001b)	IPT, 12 weeks	14 patients with MDD	25 patients with MDD given paroxetine	Resting	↓ frontal lobe
Furmark et al. (2002)	CBT, 9 weeks	6 patients with social phobia	6 patients with social phobia given citalopram and 6 patients with social phobia in WL	Anxiogenic public speaking task	↓ bilateral amygdala, hippocampus, periamygdaloid, rhinal and parahippocampal cortices in both group treated
Goldapple et al. (2004)	CBT, 15–20 sessions	17 patients with MDD	Post hoc comparison to 13 patients given paroxetine	Resting/avoiding 'ruminating'	↓ multiple frontal regions and ↑ limbic regions in CBT group ↑ multiple frontal regions and ↓ limbic regions in paroxetine group
Pasko et al. (2004)	CBT, 3 months	6 patients with panic disorder	6 distinct antidepressants	Resting	↓ R frontal and temporal regions ↑ L frontal and temporal regions
Sakai et al. (2006)	CBT, 6 months	6 patients with panic disorder	None	Resting	↓ R hippocampus, L ACC, L cerebellum, pons ↑ bilateral medial PFC
Lackner et al. (2006)	CT, 10 weeks	6 patients with irritable bowel syndrome	5 healthy subjects	Resting	↓ parahippocampal gyrus, R cingulate cortex and L pons

R: right; L: left; BT: behavioural therapy; CBT: cognitive behavioural therapy; IPT: interpersonal therapy; WL: waiting list; OCD: obsessive-compulsive disorder; MDD: major depressive disorder; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; PFC: prefrontal cortex; OFC: orbitofrontal cortex.

shown that the brain continually generates predictions and mental maps from its experience, and that they are sufficiently reliable to predict what will happen in the near future as a consequence of a given action (Graziano, Hu, & Gross, 1997). On the basis of these findings, the human brain, too, may draw maps of behaviours based on experience. Thus, memory banks constituted through objective and subjective experiences are crucial to

the human ability to generate adaptive behaviours (Baddeley et al., 2000).

All psychotherapeutic approaches articulate perception, memories, and individuals' belief systems in the therapeutic process. Perception has been studied by neuroscience, which defines it as a process of deconstruction and reconstruction of the external world on the basis of the patterns of stimulations that excite our sensory

TABLE 4
fMRI studies involving psychotherapy

<i>Study</i>	<i>Therapy type interval</i>	<i>Subjects</i>	<i>Control</i>	<i>Paradigm</i>	<i>Post-treatment decreases (↓) and increases (↑)</i>
Wykes et al. (2002)	Cognitive remediation therapy, 12 weeks	6 patients with schizophrenia, on antipsychotics	6 patients with schizophrenia given occupational therapy, 6 healthy	During working memory and vigilance tasks	↑ R inferior frontal cortex and bilateral occipital cortex
Paquette et al. (2003)	Group CBT, four 3-hour sessions	12 patients with spider phobia	13 healthy	While viewing spiders	↓ Parahippocampal gyrus and DLPFC
Nakao et al. (2005)	CBT, 12 weeks	6 patients with OCD	4 patients with OCD and fluvoxamine	Stroop test and Symptom provocation	↓ bilateral OFC, DLPFC, ACC ↑ Parietal cortex, cerebellum
Straube et al. (2006)	CBT, 2 sessions	14 patients with spider phobia	14 patients with spider phobia in WL	Symptom provocation	↓ bilateral insula, thalamus and ACC

R: right; L: left; CBT: cognitive behavioral therapy; OCD: obsessive-compulsive disorder; ACC: anterior cingulate cortex; DLPFC: dorsolateral-prefrontal cortex; OFC: orbito-frontal cortex; WL: waiting list.

receptors (Palmer, 1999). Neuroscience studies show that perception is an inferential process, too, and may be influenced by numerous factors, including psychotherapy (Nisbett & Masuda, 2003). Psychological learning processes may give rise to biological changes in cerebral synaptic activity and neurophysiological expressions (Kandel, 1998; Kandel et al., 2000, p.34). A neurobiological explanation of effective psychotherapy treatment for individuals with anxiety disorder suggests that new perceptions and corresponding memory traces are formed in a plastic brain to replace previous connections that produced anxiety reactions (Andreasen, 2004, p. 239; Paquette et al., 2003). Research on depression has also shown that psychotherapy may not necessarily lead to normalization of pathological brain activity, but may provide compensation for pathological networks by influencing other brain circuits, since some brain anomalies remain after successful treatment (Goldapple et al., 2004; Martin, Martin, Rai, Richardson, & Royall, 2001).

Therefore, neuroscience findings illustrate the importance of subjective experiences as determinants of neural reciprocities as manifest in everyday behavioural responses. The way in which we perceive and interpret the world is legitimated by the CNS, and, as we modify the latter, new neural circuits are recruited (Rainville et al., 2002). This is one of the fundamental points connecting psychotherapy and neuroscience through functional neuroimaging.

PRINCIPLES OF FUNCTIONAL NEUROIMAGING: SPECT, PET, AND fMRI

Current neuroimaging technologies have favoured recent work on the neural circuits involved in several complex cognitive functions, such as the psychotherapies used in the treatment of several disorders. These methods of investigation contributed significantly to the burgeoning relations between psychology and neuroscience with studies of the neural substrata mediators in psychotherapies (Roffman, Marci, Glick, Dougherty, & Rauch, 2005). The most frequently used methods are: single photon emission tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Some of the factors to be weighed when deciding ideal designs for studies in relation to psychotherapy are sensibility in terms of anatomical and functional detection (spatial and temporal resolution), the possibility of controlling and replicating trials, and cost and availability issues. Neuroimaging studies are mostly *structural*—examining anatomical alterations, especially those related to the volumetrics of encephalic structures—or *functional*—investigating alterations in the dynamics of cerebral blood flow, and levels of activation in neural structures and circuits. We shall now proceed to present the principles of the functional techniques most frequently used in studies involving psychotherapy.

SPECT methodology involves peripheral injection of a radioisotope deposited in the neurons and

cells of the activated glia, indicated by the dynamic blood flow response over 2–5 minutes. Neural activity tracers can specifically target a certain type of receptor in the brain in order to show its position and distribution during the resting condition, or during certain tasks determined by activation paradigms. Technetium-99m (^{99m}Tc) has a 6-hour half-life (time for half the atoms to decay from radioactive to the stable nonradioactive state) and emits 140 keV gamma radiation; with these characteristics researchers can acquire good quality experimental data with low radiation doses. The radioisotopes most often used in cerebral SPECT— ^{99m}Tc -HMPAO (hexamethylpropylene amine oxime) and ^{99m}Tc -ECD (ethylenedicycysteine)—are gamma radiation emitters. Doses are measured in terms of number of radioactive events per second, and expressed in Becquerels (1 Bq = 1 disintegration per second) or Curies (1 Ci = 37 billion Bq). HMPAO and ECD are lipophilic, so they can cross the haematoencephalic barrier. In the intracellular medium, tracers are chemically converted to hydrophilic compounds that do not cross the barrier and are retained in the cerebral parenchyma. The gamma-camera is a radioactivity detection system used to study radiomarker distribution. Images are acquired from gamma ray detectors after rotating 180–360° around the structures in question. Sections from transversal, coronal, and sagittal planes are then processed for reconstruction. The concentration of radiopharmaceutical studied per tomographic cut is directly proportional to regional cerebral perfusion—the parameter of cerebral metabolic activity. SPECT spatial resolution is 8–10 mm, which is appropriate for capturing most capillary perfusion in encephalic structures. Image acquisition is more comfortable for psychotherapy patients, and artifacts of motion are minimized.

Cerebral PET is based on obtaining tomographic images of three-dimensional distribution in the brain of certain positron-emitting radiopharmaceuticals that represent biochemical processes in vivo in relation to neural activity. Tracers are usually administered intravenously and distributed through the brain blood flow. Radioactive distribution facilitates the obtaining of images and quantitative indexes for vascular flow (^{15}O - carbon dioxide; ^{15}O - water H_2^{15}O ; ^{15}O -butanol), glucose metabolism (^{18}F -deoxyglucose—FDG), oxygen consumption (^{15}O), and activation of several neuromediators (^{18}F -DOPA; ^{18}F -spiperone; ^{18}F -raclopride; ^{18}F -flumazenil). The relatively short half-life of markers with energy around 500 keV requires a cyclotron near the acquisition camera to produce them. Most PET images in

psychotherapy are acquired with ^{15}O (half-life 1–5 minutes) or FDG (half-life 30 minutes) tracers. When these radioisotopes decay, they emit positrons that can then collide with electrons, producing gamma ray photons. The two gamma rays resulting from this nuclear reaction are paired and emitted from the nuclide in opposite directions (at 180°). Photons are recorded by orbital heads (set up to capture only particles at 180°) and images are then reconstructed with the precision of the point of origin of the photon. FDG takes 30 minutes to produce an integrated image of brain activity, which is slow for the requirements of most neuropsychological activation experiments; however, the acquisitions do provide a robust portrayal of the distribution of brain activity in the basal state, or during ongoing cognitive task performance. PET provides 4 mm spatial resolution and greater precision than SPECT for capturing capillary perfusion. PET advantages include sensibility to very low concentrations of neuromediators and its ability to provide quantitative information with a relatively quiet procedure. The procedure for radiation exposure during PET or SPECT is similar to radiological diagnosis. Nevertheless, special precautions are required when using radiopharmaceuticals in research protocols, and the risks must be explained to those involved in the context of obtaining informed consent.

fMRI uses the BOLD (blood oxygen level-dependent) effect to trace neural activity. Surges in blood flow occur in response to increased local neural activity, which demands oxygen from within blood cells. Oxygen is transported by oxyhaemoglobin molecules (with diamagnetic Fe) and deoxyhaemoglobin (paramagnetic Fe), and excess blood oxygen leads to a relative decrease in deoxyhaemoglobin concentration in capillaries and venules draining blood from the tissue. The magnetic gradient in blood cells varies in relation to the free blood around them. Subtle alterations between oxygenated and deoxygenated haemoglobin are detected as variations in magnetic signal, which reliably reflects variations in cerebral blood flow, as indicators of changes in local cerebral activity. The steeper the magnetic field gradients, the more precision there will be in reception of subtle paramagnetic signals. Most magnetic resonances generate a field of 1.5 Tesla (T) and protocols are currently carried out in equipment rated 3T, 4T (and experimentally 7T and 15T), with submillimeter resolution. Acquisition speed for fMRI has been greatly enhanced by echo-planar imaging (EPI) coils capable of acquiring ultra-fast images of the entire brain from multiple

cuts in a few seconds. Temporal and spatial resolution (3 seconds and 1–3 mm respectively) feature fundamental gains in relation to SPECT and PET techniques for studying human cerebral functioning during mental activity, which may be anatomically co-recorded in the same series of data acquisition. The fMRI method can also assess responses related to a single short-term event, so researchers can use experimental designs in which the course of specific responses may be accurately marked amidst responses related to other stimuli. Another advantage is that the technique is noninvasive, so there is no limit to the number of trials per subject.

In short, both SPECT and PET use radioisotopes to trace regional metabolic alterations in brain blood flow. In addition to measuring the dynamics of capillary perfusion in the brain and glucose metabolism as indicator of neural activity, these methods are also used to study receptors and neurotransmitters involved in psychopathologies, since they allow the use of different tracers. fMRI is noninvasive and can combine high resolution imaging of brain blood flow alterations with anatomical images. The method makes use of the paramagnetic properties of deoxyhaemoglobin to mark haemodynamic responses through changes in blood oxygenation—the BOLD effect—which are also indicative of neural activity. Voxel-based measurements may also be acquired using fMRI. The above neuroimaging methods can measure neural activity by monitoring energy supplements released through synaptic activity. This is one of the factors affecting temporal resolution in SPECT, PET, and fMRI techniques. However, techniques monitoring variations in cerebral electrical activity, which is directly related to synaptic activity, can achieve high temporal resolution. Nevertheless, no one method is ideal in terms of meeting the requirements for investigating neural substrata mediating psychotherapy effects (see the main advantages and limitations of the three most common methods in Table 1).

FUNCTIONAL NEUROIMAGING AND PSYCHOTHERAPY

SPECT, PET, and the fMRI were initially used to evaluate neural correlates involved in psychotherapy (see Tables 2, 3, and 4) for individuals with obsessive-compulsive disorder (Baxter et al., 1992; Brody et al., 1998; Nakao et al., 2005; Nakatani et al., 2003; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996), major depressive disorder (Brody

et al., 2001a, 2001b; Goldapple et al., 2004; Martin et al., 2001), social phobia (Furmark et al., 2002), specific phobia (Johanson, Risberg, Tucker, & Gustafson, 2006; Paquette et al., 2003; Straube, Glauer, Dilger, Mentzel, & Miltner, 2006), panic disorder (Prasko et al., 2004; Sakai et al., 2006), schizophrenia (Penades et al., 2002; Wykes et al., 2002), post-traumatic stress disorder (Levin, Lazrove, & Van der Kolk, 1999; Peres et al., in press), and irritable bowel syndrome (Lackner et al., 2006). The results in general show that the psychotherapeutic approaches used had the potential to modify dysfunctional neural circuits associated with the disorder in question. Psychotherapy influenced neuropsychological normalization with a corresponding development of the patient's psychological equilibrium. In fact, changes occurring at the mental level through psychotherapy are accompanied by changes in brain blood flow and normalization of patients' neural dynamics (Gabbard, 2000; Rybakowski, 2002). The title of a University of Montreal study of the use of cognitive therapy to treat arachnophobia aptly quoted the expression "Change the mind, and you change the brain" (Paquette et al., 2003).

Studies published to date have noted the advantages and limitations of neuroimaging methods (Table 1) and controlled experimental design using manual-based treatment in a time-limited setting (Table 2, 3, and 4). We shall now examine some key factors involved in designing studies involving psychotherapy and neuroimaging.

Prerequisites for experimental designs

In functional neuroimaging, brain activation levels must be viewed in relation to one or more circumstances. The logic of subtraction (comparison of two events that putatively differ by only one factor) (Donders, 1969) is critical for correct attribution of significance of the activation levels observed. The logic of subtraction relies on the assumption of pure insertion (two circumstances differ in one critical component and one only). If this assumption is false and there are multiple differences, then it will be impossible to distinguish the value and significance of data obtained. Thus, choosing the best baseline condition that will subtract all activation except that relevant to the study is crucial to successful functional neuroimaging research.

Studies involving psychotherapy and neuroimaging should preferably be hypothesis driven. They should be based on full knowledge of the disorder and the corresponding neurobiology, as well as the

expected outcome of neurofunctional normalization brought about by psychotherapy. Researchers plan studies with certain expectations regarding findings arising from the circumstances of subtraction. Statistical tests are then performed to determine whether expected differences exist or are unlikely. Nevertheless, interfacing between functional neuroimaging and psychotherapy is still at an embryonic stage; much research has yet to be done in relation to the neural substrates involved in psychiatric disorders, so researchers should avoid rigidly pre-determined hypotheses. A different approach is the data-driven study without an a priori assumption predicting neural activity patterns. Yet another (even more convenient) strategy is to analyse independent components to extract variability from the data obtained in hypothesis-driven testing, often surprising the investigator with unexpected data that pose new hypotheses (Biswal & Ulmer, 1999). Two main approaches are used in experimental designs for these studies: voxel counting (VC) and regions of interest (ROI). The former involves performing a statistical comparison between two (or more) conditions of interest based on voxel counting without prior assumptions as to the specific areas of the brain to be differentially activated. The brain may be investigated as a whole without generating detailed hypotheses on predicted focuses of activation. The ROI approach directs attention to regions previously described and pre-determined as related to certain cognitive tasks for more investigation. For instance, the hippocampus is one of the ROIs in protocols that involve memory, because there is previously established knowledge of its involvement in this cognitive process.

Careful choice of functional neuroimaging methods is required in studies involving psychotherapy. Localization of neural circuits will be valuable only when they provide data pertinent to validation or construction of theories relating to the cognitive function being studied. Therefore, this information may guide hypotheses toward more assertive interventions in relation to the disorder studied. Certain types of functional studies may make specific contributions in this sense, beyond what may be learned from other methods of investigation. Some examples follow.

Comparisons of the same neural activity through multiple tasks

Data obtained for similar neural activities triggered by different tasks may pose relevant contributions to therapeutic approaches aimed at stimulating skills lost through illness or neurological trauma. Corbetta et al. (1998) showed that

ocular movements and attention shifts evoked network activation in almost equivalent brain networks. These experimental designs may lead to findings on dissociation or association for activation of similar circuits, and neuropsychology will certainly gain elements that may be used to guide interventions (James, Culham, Humphrey, Milner, & Goodale, 2003). In relation to psychotherapy, we would mention the example of individuals with post-traumatic stress disorder (PTSD) who had difficulty in integrating sensory fragments in a resilient (prefrontal dependent) narrative (Halligan, Michael, Clark, & Ehlers, 2003), although their declarative memory systems were fully functional for nontraumatic events. There were no differences between PTSD patients and control subjects for brain activation patterns during retrieval of neutral memories (Bremner et al., 2003; Wessa, Jatzko, & Flor, 2006). Since multiple memory systems may be activated simultaneously and in parallel and may also interact on various occasions, psychotherapy may prompt the retrieval of resilient emotional memories and facilitate integration of sensory fragments in a (prefrontal dependent) declarative memory system (Peres, Mercante, & Nasello, 2005a).

Characterization of responses from a single region of interest

Functional neuroimaging may be used to identify the activity of a single area according to the incentives and tasks that are hypothetically correlated with this ROI. For instance, certain studies have identified the key areas for recognition of human faces (Kanwisher, McDermott, & Chun, 1997) and more detailed hypotheses were then generated as to how facial recognition is processed in the brains of healthy or impaired individuals (Hadjikhani et al., 2004; Hasson, Avidan, Deouell, Bentin, & Malach, 2003).

Neural correlates of behaviors

Studies may go beyond the measurement of basal metabolism by acquiring both symptom-specific behavioural data and functional data at the same time. On this basis, neural correlates of the behaviour produced may be examined. A good example of this approach is seen in symptom provocation paradigms used to investigate phobic behaviours before and after psychotherapy (Furmark et al., 2002; Paquette et al., 2003).

Neural evaluation of experience and learning

Studies on different levels of experience or training may help distinguish innate processes and processes of plasticity derived from experience. Neural comparisons between experienced and non-experienced individuals executing the same task (Gauthier, Skudlarski, Gore, & Anderson, 2000) may help compile useful designs for psychotherapy by leveraging the fMRI facility of performing repeated noninvasive trials. Studies of long-term practice and task complexity in musicians and nonmusicians have provided a useful model of neuroplasticity. Practice and learning led to robust effects in terms of plastic brain changes with implications for cortical organization (Meister et al., 2005). Learning derived from psychotherapeutic experience may also modify neural expressions (Kandel, 1998). Well-elaborated designs will provide an understanding of the neural correlates involved in the efficacy and/or inefficacy of therapy. These findings may guide more assertive interventions for balancing deficient neural activities in specific disorders (Peres, Mercante, & Nasello, 2005b).

Identification of specific symptoms in the brain

Some pathologies express episodic rather than constant symptoms, sometimes lasting a few seconds, such as in Tourette's Disorder cases. Neuroimaging enables us to observe the human brain during episodic cognitive disorder, helping to explain unusual functional dynamics in specific patient populations. For instance, Dierks et al. (1999) found activation of the auditory cortex in schizophrenic patients while hearing voices. fMRI related to events can provide very specific data acquisition, and signalling methods may be coupled to PET- and SPECT-based studies to control for neural activity corresponding to the point in time reported by the subject. For instance, Newberg, Alavi, Baime, and D'Aquili (1997) investigated a specific state of consciousness during a complex task of meditation signalled by specialists submitted to the study. Similar designs of interest for psychotherapy may be developed.

Functional design in psychotherapy

Producing an effective design for comparing neural substrata before and after psychotherapeutic intervention is a challenge that requires particular care. Emotional tasks combined with

complex cognitive states may involve considerable risk in relation to the interpretation of findings. A subject's expectations in relation to acting correctly may contaminate neurofunctional findings. Researchers have to control variables in order to measure the specific effect of psychotherapy. Activation paradigm designs must be simple, objective, and favour real reflection of emotional states investigated in subjects submitting to psychotherapy. Control groups must be selected carefully to ensure that subtraction of the target group is based on a reliable benchmark. Another crucial precaution relates to the interval between functional measurements. Neuroimaging protocols that evaluate neural correlates before and after psychotherapeutic intervention should ideally have an 8-week interval between neuroimaging data acquisitions. In relation to occurrence-relevant variables influencing outcomes of psychotherapy, control for a period of more than 12 weeks becomes questionable. Numerous variables arising from the time factor (new events, incidents, other interventions by relatives, colleagues, religiosity, etc.) may contaminate outcomes. Although some studies have been performed over periods of 6 months or more (Sakai et al., 2006), we suggest that researchers should consider shorter periods.

Concerning experimental design, one of the most important challenges is the question of which parameters to control in order to measure the effect of psychotherapy: symptoms, perception, beliefs, internal dialogues, autonomous physical responses, or others. Baxter and colleagues reported the first study involving psychotherapy and neuroimaging in 1992. Previous functional neuroimaging studies had already shown increased right caudate activity in patients with obsessive-compulsive disorder (OCD). PET was used to study individuals with OCD divided into two groups, Behaviour Therapy and Fluoxetine, and both groups showed a decrease in right caudate activity after treatment (Table 3). No activation paradigm was used and subjects were in repose during scans. This design influenced most of the subsequent studies (Tables 2, 3, and 4). Current research work tends to go beyond measuring basal metabolism. Since diminishing symptoms is in general a key aim for psychotherapies, recent studies have used activation paradigms to provoke symptoms in scans before and after psychotherapy (see fMRI studies in Table 4).

As an example of advances in PTSD diagnosis and treatment arising from the fruitful interface between neurosciences and psychotherapy, methods for temporarily inducing symptoms have led to reliable reports of psychoneurophysiological

changes in individuals with PTSD (Bremner et al., 1999; Lanius et al., 2002; Pitman, Orr, Forgue, De Jong & Claiborn, 1987; Rauch et al., 1996; Shin et al., 2004). PTSD symptoms were experimentally induced using script-driven imagery, sound, virtual reality devices, cognitive activation paradigms, and anxiogenic pharmacological agents. Symptom-provoking paradigms measured brain functioning while controlling for the most commonly manifested symptoms and mental states in the psychopathology in question. Most were subdivided into three groups, using sight and hearing as sensory-perception channels to trigger symptoms: (I) presenting figures or films, (II) presenting noises and sounds, and (III) presenting general or personalized memory-evoking scripts. These studies usually interposed symptom-provoking stimuli with neutral stimuli in planned (but randomized) sequences. We emphasize that these same principles may be used in psychotherapy-neuroimaging studies to identify neural reciprocities pertinent to diminishing symptoms by comparing pre- and post-psychotherapy scans. Statistically significant results in relation to increased or decreased neuronal activity were obtained by subtracting the subjects' control (neutral) states from the activation (symptom manifestation) state. Healthy volunteers were often used in control groups to perform identical tasks for comparison with activations obtained in individuals with psychopathology (patients may be compared with healthy controls to see whether brain activity is abnormal prior to treatment and "normalizes" after psychotherapy). Additionally, control conditions such as placebo, or other active treatment groups, may be useful in evaluating the unique neural changes that may be attributed to a specific form of psychotherapy. The neuroimaging methods and experimental designs used, drug-naïve or drug-free status of patients, their comorbidities, patient-therapist interaction, and adherence are all crucial variables that must be controlled in order to produce "cleaner" comparisons between psychotherapeutic methods in the future.

Research designs should be standardized so that we can compare the efficacy of different approaches used for a specific disorder. We therefore suggest a simple model for designs on the following lines. (1) DSM-IV screening to select disorder patients to be studied, and healthy volunteers. Administering scales specifically for disorder symptoms for prospective evaluation. (2) Random distribution of patients (profile matched) in three groups: one subjected to psychotherapy (experimental group) and the other two not (controls—waiting list, placebo, other intervention, etc.). (3) Initial scanning of the three groups. (4) A defined period of

therapy. (5) Second scan of the three groups. (6) Readministration of the psychological measurements/scales used in phase 1 and assessment of responding and nonresponding patients in the group subjected to psychotherapy. (7) Data processing and statistical analysis (multiple comparison), using scores on scales as statistical regressors and evaluating connectivity analysis.

Neuroscience findings and PTSD: Implications for psychotherapy

We would emphasize that neuroimaging-psychotherapy studies should use previous findings to formulate hypotheses in relation to the satisfactory effects of psychotherapeutic interventions. We found a good example of this in studies of individuals with PTSD. CNS failures in interpretation, synthesis, and integration of emotionally impacting and painful episodes play a critical role in experiences perceived as traumatic (Van der Kolk, 1997). Neuroimaging studies have replicated some findings relevant for the understanding of structural and functional abnormalities associated with PTSD. The difficulty of synthesizing, classifying, and integrating a traumatic memory as part of a narrative may be related to a relative decrease in hippocampus volume and activation and decreased activity in the prefrontal cortex, anterior cingulate, and Broca's region (Bremner et al., 1999; Gilbertson et al., 2002; Lanius et al., 2002; Shin et al., 2004). Deficient means of extinguishing responses to fear and emotional deregulation may be related to lower levels of prefrontal cortical activity, and reduced negative feedback may be related to amygdala activity. These non-hippocampus/prefrontal-dependent traumatic memories are accessed involuntarily; they are presented fragmented in sensory traces and tend to remain with intense emotional expression and vivid sensations (Lanius et al., 2002; Shin et al., 2004). Psychotherapeutic processes based on exposure and cognitive reconstruction (Marks, Lovell, Noshirvani, Livanou, & Thrasher, 1998) may stimulate the cognitive and integrative faculties of the brain corresponding to deficient structures in PTSD individuals. From this perspective, the memory may diminish in emotional intensity and be more cognitively organized (Peres et al. 2005b, Peres et al., in press).

There are other neuroscience findings showing that emotion-charged memories are not static but are interpretations or new versions reconstituted from the original event (Jones et al., 2003). Rather than factual traumatic memories, the brain stores traces of memory used in neural circuits to

reconstruct memories, not always faithfully expressing the past experience (Baddeley et al., 2000). Squire and Kandel (2003, p. 90) note that remembering involves the reconstruction of a coherent plot from available fragments. Furthermore, the most important regulators and modulators in the acquisition, formation, and evocation of memories are emotions and level of consciousness (Dolan, 2002). Studies reveal that retrieval of traumatic memoirs occurs in an altered state of consciousness with major emotional expression (Bremner et al., 1999; Van der Kolk, Burbridge, & Suzuki, 1997). Once the state of consciousness is modified, perception of the same event also undergoes changes (Dietrich, 2003), so there is a new interaction and relationship in the context being coped with by the trauma victim. On the basis of neuroscience findings taken as a whole, psychotherapeutic approaches may revisit and align their interventions for the treatment of traumatic memories. For instance, psychotherapists must be able to work with emotions and altered states of consciousness that directly modulate the formation of memory. Moreover, they may make good use of the CNS's faculty for cognitively reinterpreting and reconstructing emotionally charged memories for psychotherapeutic effects (Peres et al., 2005a, in press).

LIMITATIONS

Inter-individual differences in processing life events and basic emotions are probably co-responsible for inconsistent findings across different studies (Eugene et al., 2003). Symptom homogeneity, nonspecific factors relating to psychotherapists and the nuances of the methods used, as well as qualitative processing of subjective experiences, are hard to control for and are complex factors in neuroimaging studies.

Familiarity with equipment should also be controlled, so that a volunteer's attention can be focused on the procedure. This is not always the case, due to the cost of neuroimaging equipment or lack of access to it for training subjects in situ. When subjects are assigned a task that may be contaminated by complexity, expectation of success and/or distraction, or avoidance strategies used in the scanner, researchers may obtain neuronal findings related to these variables. The psychotherapy setting, too, should be controlled. Depending on the activation paradigm used in the protocol, maintenance of the therapeutic setting is an important variable to be controlled. SPECT is the only neuroimaging method that enables researchers to maintain the natural psychotherapy

setting. The longer radioisotope half-life—4 to 6 hours—and the image acquisition method mean that the tracer may be introduced outside the hospital, as long as aseptic precautions are taken; after a few hours gamma-camera acquisitions may proceed in the hospital's nuclear medicine unit.

Synaptic chemicals process communications in milliseconds, with a rich modulation of information for opening and closing different channels of the cellular membrane. These operate analogically in synchronism with a range of neuromodulators (aminoacids, amines, and peptides). Whenever a behaviour is initiated, we simultaneously activate and deactivate neural networks, and thousands of excitatory and inhibitory synaptic discharges occur in the process. Neural circuits perform cognitive tasks in milliseconds, but the temporal resolution of neuroimaging methods cannot keep up with this real-time processing. So records are faithful but partial, and the occurrence of neural activity is identified in seconds or minutes.

CONCLUSION

There has always been a connection between psychotherapy and neural activity, but we now have the methods with which to understand these correlates. Despite the dichotomy between psychology and medicine in the past, the 21st century poses a special opportunity for their convergence through neuroscience. Questions relating to the neurobiological effects of psychotherapy are now viewed as some of the most relevant issues for neuroscience. That psychotherapy is capable of producing detectable changes in the brain is no longer at issue. Most comparisons of pharmacological and psychological interventions (except Goldapple et al., 2004) have found rather similar effects on cerebral metabolism. Growing numbers of *neuroscientist-psychotherapists* have been building bridges between these complementary and interdependent areas of knowledge. However, although neuroimaging has proved to be an important means to advances in understanding, diagnosis, and treatment of psychopathologies, the fascination of new technology may obscure the fact that we are still at an embryonic stage. We are a long way from being able capture the complex flows of information moving through neural networks. Rather like the early camera, with a front-end pinhole backed by slightly light-sensitive silver nitrate, functional neuroimaging methods record only the slowest and most stable data. Low temporal and spatial resolutions pose major limitations for capture of the complex neural

filigree, which we will be able to record better in the future. Multimodal methods integrating the specificity of PET tracers, the anatomical definition of MRI, and the temporal resolution of qEEG are now being introduced, although the costs are still too high for widespread scientific use. Future studies will examine the specificity of the functional, structural, and neurochemical/molecular substrata required for our understanding of the physiopathology of mental disorder. However, the neurophysiopathology of these disorders may be dynamic, and neural correlates may vary over time in their expression. It seems certain that advances in technology will gradually lead to more accurate identification of neural circuits associated with certain disorders. Current and future findings should provide guidance for psychotherapeutic interventions in relation to what to stimulate in individuals in order to normalize deficient neural activities. The better our understanding of the significance of the results obtained by neuroscience, and the more data collected, the more useful these contributions will be for psychotherapeutic intervention.

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