Neuroplasticity and the brain connectome: what can Jean Talairach's reflections bring to modern psychosurgery?

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Contrary to common psychosurgical practice in the 1950s, Dr. Jean Talairach had the intuition, based on clinical experience, that the brain connectome and neuroplasticity had a role to play in psychosurgery. Due to the remarkable progress of pharmacology at that time and to the technical limits of neurosurgery, these concepts were not put into practice. Currently, these concepts are being confirmed by modern techniques such as neuroimaging and computational neurosciences, and could pave the way for therapeutic innovation in psychiatry.

Psychosurgery commonly uses a localizationist approach, based on the idea that a lesion to a specific area is responsible for a deficit opposite to its function. To psychosurgeons such as Walter Freeman, who performed extensive lesions causing apparently inevitable deficit, Talairach answered with clinical data: complex psychic functions cannot be described that simply, because the same lesion does not provoke the same deficit in different patients. Moreover, cognitive impairment did not always follow efficacious psychosurgery. Talairach suggested that selectively destructing part of a network could open the door to a new organization, and that early psychotherapy could encourage this psychoplasticity. Talairach did not have the opportunity to put these concepts into practice in psychiatric diseases because of the sudden availability of neuroleptics, but connectomics and neuroplasticity gave rise to major advances in intraparenchymal neurosurgery, from epilepsy to low-grade glioma. In psychiatry, alongside long-standing theories implicating focal lesions and diffuse pathological processes, neuroimaging techniques are currently being developed. In mentally healthy individuals, combining diffusion tensor imaging with functional MRI, magnetoencephalography, and electroencephalography allows the determination of a comprehensive map of neural connections in the brain on many spatial scales, the so-called connectome. Ultimately, global neurocomputational models could predict physiological activity, behavior, and subjective feeling, and describe neuropsychiatric disorders.

Connectomic studies comparing psychiatric patients with controls have already confirmed the early intuitions of Talairach. As a striking example, massive dysconnectivity has been found in schizophrenia, leading some authors to propose a "dysconnection hypothesis." Alterations of the connectome have also been demonstrated in obsessive-compulsive disorder and depression. Furthermore, normalization of the functional dysconnectivity has been observed following clinical improvement in several therapeutic interventions, from psychotherapy to pharmacological treatments. Provided that mental disorders result from abnormal structural or functional wiring, targeted psychosurgery would require that one be able: 1) to identify the pathological network involved in a given patient; 2) to use neurostimulation to safely create a reversible and durable alteration, mimicking a lesion, in a network compatible with neuroplasticity; and 3) to predict which functional lesion would result in adapted neuronal plasticity and/or to guide neuronal plasticity to promote recovery. All these conditions, already suggested by Talairach, could now be achievable considering modern biomarkers and surgical progress.

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ABBREVIATIONS DBS = deep brain stimulation; DTI = diffusion tensor imaging; ECoG = electrocorticography; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation.

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FIG. 1. A: Walter Freeman and Henrique João de Barahona Fernandes at the First World Congress of Psychiatry. **B:** Henri Ey. **C:** Jean Talairach. Courtesy of the Henri Ey Library collection, Sainte-Anne Hospital (A and B), and the private collection of Gerard Proust (C).

GREAT thinkers often point out revolutionary concepts long before they had the scientific tools to verify them. Dr. Jean Talairach (1911–2007; Fig. 1C), whose stereotactic brain atlas and pioneering contribution to epilepsy surgery won him a place in the neurosurgical “Hall of Fame,” was also a remarkable psychosurgeon and theorist^{14,81,82} (Fig. 2).

The examination of what he imagined and wrote in the 1950s is of great interest now that psychosurgery is making a comeback due to the difficulty of finding new pharmacological agents, but also due to the progress made in surgery and neurosciences. Therefore, the first goal of this paper is to describe the hypotheses Talairach developed

in 1952 about what is now called the brain connectome and neuroplasticity applied to psychosurgery, just before abandoning psychosurgery to devote himself to epilepsy surgery. We argue that these hypotheses, which have been neglected for decades, are now confirmed by modern techniques such as neuroimaging and computational neurosciences, and could provide the foundation for therapeutic innovation in psychiatry.

A Localizationist Theory of Psychosurgery

Jean Talairach started his career as a psychiatrist in 1940 at Sainte-Anne Hospital (Fig. 3), Paris, before the

FIG. 2. A: Operating theater in Sainte-Anne Hospital. **B:** Jean Talairach performing a surgical procedure. Courtesy of the Henri Ey Library collection, Sainte-Anne Hospital.

development of neuropharmacology. Because treatments were limited in this field, he turned to surgery to find new therapeutic options for his patients. At that time, all psychosurgical interventions were based on localizationist concepts, which classically stipulates that a particular area of the brain is in charge of a particular function. The one exception was capsulotomy that was only developed in 1949,⁶⁵ which does not correspond to a neocortical lesion, but targets the white matter prefrontothalamic projections in the anterior limb of the internal capsule.

The 19th century “localizationism-equipotentialism” controversy, led by the Broca⁹ and Flourens³³ schools, which concerns the organization of the brain, led to major advances in neurology. Localizationism constituted the first tool to locate tumors, based on the work of Hughlings Jackson, which correlated clinical examination and brain location of the lesion. William Macewen⁶⁰ performed the first intracranial tumor resection.

The localizationist approach in psychosurgery was inherited from the work of Karl Kleist, who produced a functional atlas of cortical function⁵⁶ based mainly on the observation of patients with traumatic brain injuries who showed various types of what we would now call frontal syndrome. The basic idea was that a post-lesion deficit indicates that the lesion occurs in a location responsible for a function opposite to the deficit. For example, a basifrontal

lesion producing euphoria would indicate that anxiety is located in this area because some authors believed that anxiety was the opposite of euphoria.⁵⁵

Developing the theory, Walter Freeman (Fig. 1A) introduced the notion that mental disorders were progressive along this localizationist organization.⁸¹ The more sophisticated the function, the more anterior the frontal location. Considering that psychiatric disease always started by affecting the area related to personality, and therefore in the “superior” frontal location, the evolution of the pathology was supposed to be related to an anatomical posterior spreading.³⁹ Consequently, when he performed frontal leucotomies for mentally ill patients, he encouraged early surgical interventions to limit the destruction of supposedly responsible brain locations and therefore deficits. Quite logically, the longer the evolution was, the more posterior he recommended to extend the leucotomy.^{37,89}

Talairach Criticism and New Concepts

Jean Talairach strongly criticized Walter Freeman’s and James Watts’s localizationist conception underlying their psychosurgical procedure.⁸¹ Clinical examination was unquestionable: if the brain was truly and fully organized in a localizationist way, then a lesion should produce a reproducible and constant deficit, as is the case for primary areas such as the motor cortex or the primary visual area, in which a lesion always leads to the same symptoms. Yet in large series available at that time, including 331 patients reported on by Walter Freeman himself in 1946,³⁸ this was not the case.

Talairach also supposed that the more complex a function is, the more brain areas or networks are involved. According to him, this would explain why cognitive or psychiatric dysfunctions are not directly correlated with the size of a lesion, such as dementia with the severity of prefrontal atrophy (even if with modern imaging, recent findings have found a correlation without causality between these elements), or general paresis delirium with the extent of syphilitic encephalitis. Complex functions would therefore be much more complex to understand and describe.

In reaction to the limits of these mechanistic theories, Jean Talairach supported and developed Henri Ey’s organodynamic theory^{28,29} (Fig. 1B). This theory was the result of Jacksonian hierarchical organization of the CNS applied to the field of psychiatry.³⁰ It suggested that the brain was an integrated network rather than a juxtaposition of localized elementary functions. A lesion was thus responsible for the alteration of multiple functional sub-networks involving distant regions of the brain. Henrique João de Barahona Fernandes (Fig. 1A) suggested that a lesion produced a dissolution of the functions supported by the impaired network and was followed by a compensatory reintegration,⁶ which we would call neuroplasticity.

However, Barahona Fernandes believed that this compensatory reintegration of the impaired functions led to a psychic regression, which was even necessary for the treatment to be effective in patients after frontal lobotomy.⁵ Conversely, based on several observations that he and other psychosurgeons had made, Talairach showed that

FIG. 3. Photographs of Sainte-Anne Hospital main entrance (A) and surgery pavilion of Sainte-Anne Hospital (B), both from the 1950s. Courtesy of the collection of the museum of Sainte-Anne Hospital.

the postsurgical intellectual decrease was often absent and therefore unnecessary to psychiatric improvement (“Fait capital pour nous, il est des cas de malades complètement guéris chez lesquels il est impossible de retrouver trace d’un déficit quelconque, intellectuel ou affectif [...] Ceci prouve que la présence du syndrome régressif ou déficitaire définitif n’est pas nécessaire à la guérison.”⁸¹). He suggested that surgically targeted lesioning, if not too extensive, could lead to the destruction of a network and open the door to a new organization (“La lésion ayant perturbé ou détruit certains appareils fonctionnels, en ayant libéré et désorganisé d’autres, il se produirait sur le plan de l’organisme une nécessité d’adaptation nouvelle.”⁸¹).

In contrast to electroconvulsive therapy (ECT), for instance, psychosurgery could produce a targeted and durable lesion that would allow a slow reorganization. This reorganization would be the crucial opportunity to treat mental disorders. Talairach emphasized the importance of limiting the size of the lesion to create the possibility of reorganization without impairing the recovery capacity by damaging the networks too extensively.⁸¹

Talairach did not have the opportunity to put these concepts into practice in psychiatric diseases because of the sudden availability of neuroleptics in the same place at the same moment,¹⁸ but he successfully did so in epilepsy surgery. Ironically, Sainte-Anne Hospital was not only a pioneering center of psychosurgery, but also a major center for neuropharmacology. In 1952 Jean Delay and Pierre Deniker opened a new era of psychiatry by describing the effect of chlorpromazine¹⁸ (the first antipsychotic) in schizophrenia. Consequently, Talairach quickly abandoned his work in psychosurgery to focus on epilepsy surgery.

Talairach revolutionized the field of epilepsy surgery with the same concepts: whereas awake surgery and peri-

surgical electrocorticography (ECoG) were used as tools to help resections, he considered epilepsy a dynamic process within a pathological network rather than a focal cortical pathology.⁸³ That is why he developed stereoelectroencephalography to provide a long recording period of pathological epileptic networks during and between seizures, and stop focusing on perioperative interictal ECoG abnormalities.

How Hodotopy and Neuroplasticity Have Proved True and Helpful in Intraparenchymal Neurosurgery

Intraparenchymal neurosurgery in general has been largely dominated by localizationist concepts until recent decades. Resection was limited by “eloquent areas” or “functional regions” constituting no-go zones. The development of the concept of the brain connectome organized in an hodotopic way, and a better comprehension of the mechanisms underlying neuroplasticity, led to major changes.^{16,22,23}

The hodotopic (from the words “hodologic” and “topic”) model of the brain is a notion resulting from the integration of the topic organization of cortical functional nodes with a hodological organization corresponding to their interconnections by large-scale white matter tract networks.¹⁵ This model is sustained by distributed dynamic neural processes on multiple spatial and temporal scales.^{49,79} This model fits with the anatomical findings in healthy subjects and patients,^{7,50} which define the brain connectome and its essential hubs that are crucial for recovery.^{46,51} Extensive work on the most studied functions in intraparenchymal function have led to a more and more accurate description of this anatomy.

For example, the inferior frontooccipital fasciculus,³ frontal aslant tract,⁵⁴ uncinate fasciculus,¹³ inferior longitudinal fasciculus,³ different portions of the arcuate fasciculus,^{13,61} and the way they interconnect with the past classic “eloquent cortical area” of language, are at least as important as the cortical functional anatomy to understand the possibility of recovery after surgery. Following this example, an extensive surgery of the left temporal pole involving the inferior longitudinal fasciculus and uncinate fasciculus (i.e., the core of the “indirect semantic ventral pathway”) produces semantic troubles that will recover within a few weeks or months, only if the left inferior frontooccipital fasciculus is preserved (i.e., the core of the “direct semantic ventral pathway”).^{25–27} Furthermore, when such a network is impaired, for example by a tumor, and a semantic difficulty exists before surgery, tumor removal can lead to an improvement of language.⁷⁵ Preservation of the connectome is thus crucial to restore normal function after surgery and to allow an improvement of an altered function by means of neuroplasticity and new weighting within the preserved network. Evidence of such functional reshaping in the connectome following surgery is not only supported by clinical observations; more and more noninvasive investigations, such as functional MRI, tend to corroborate these findings.⁸⁸ More than the definition of a limited number of “core structures” on an artificially limited number of “major functions,” the major advance is represented by the comprehension of the architecture of the connectome and its subnetworks.²⁴

When Jean Talairach wrote that destructing a pathological area could free another one, he did not give any precise surgical example, but later epilepsy surgery showed that resecting a pathological hippocampus could improve memory,⁸ which proves once again that discharging networks from a distant pathological burden can help gain function and that lesioning surgery does not have to lead to a loss of function to be effective. Nevertheless, evidence is lacking to determine if this improvement is the consequence of the seizure no longer spreading to the contralateral hippocampus and along the limbic system, or due to a remodeling of the connectome following resection.

This connectomic approach makes sense because neuroplasticity plays a part: it is a continuous process allowing both short- and long-term remodeling of the neuronal synaptic organization.²³ Recovery would then be related, among other factors, to the preservation of the subcortical pathways of the connectome, which allows a redistribution within the preserved networks.¹⁹ Applied to intraparenchymal surgery, which corresponds to an acute brain lesion, this lead to procedures sparing the essential hubs of the connectome to avoid permanent deficits.^{23,52}

The 3 main advances are thus to avoid and/or predict postoperative deficits, to make sure that the expected deficits will be recovered within a few weeks or months, and to restore or improve a function altered preoperatively. This last point is the relevant one for the development of new psychosurgical approaches.

Talairach also had the intuition that neuroplasticity after a surgical intervention could take months, and highlighted the importance of performing psychotherapy when neuroplasticity was active in the same way that mo-

tor physiotherapy is crucial after a central motor deficit. These concepts, although largely used currently in intraparenchymal surgery, are not yet the common approach in psychosurgery, but new therapeutics will certainly emerge from them soon.

Connectome Dysfunction in Psychiatric Disorders

Since the beginning of the 20th century, pathophysiological theories in psychiatry rapidly evolved from focal lesions to diffuse pathological processes. Even localizationist theories, such as Wernicke’s sejunction hypothesis,⁸⁵ relied on diffuse lesions of association fibers leading to impaired interactions between brain regions. In fact, a tremendous effort was dedicated to the quest of the histological hallmark of schizophrenia, which was eventually considered to be the “graveyard of neuropathologists.”^{64,73}

Neuroimaging techniques such as diffusion tensor imaging (DTI) allow researchers to dissect structural connectivity, which is to say the architecture and the global organization of white matter fiber tracts. To study such an impressive amount of data, powerful tools of graph theory are often used to extract the general properties and relevant features of the brain network.^{10,11} Brain regions are thus represented as nodes while neuroimaging is used to compute a measure of association between nodes (e.g., connection probability using DTI even if a functional connectivity measure could also be used) resulting in a matrix of all possible pairwise associations. After thresholding, topological properties of the network can be extracted such as mean path length (mean number of steps to go from one node to another) or connection density (actual number of connections over the total number of possible connections) resulting in a quantitative description of the brain network. The same mathematical tools may be used with functional connectivity (statistical dependence of neurophysiological neural signals between brain regions) and effective connectivity (the impact of the activity of one region on another one). Combining DTI with functional MRI, magnetoencephalography, and EEG could thus allow the determination of a “comprehensive map of neural connections in the brain on many spatial scales,”⁷⁹ the so-called connectome.^{34,59,78,79} Note that the connectomic approach is also a critical step in building models linking structure to function. Indeed, brain structure may be used as constraints on computational models describing cognitive mechanisms underlying behavior. Ultimately, one could devise global neurocomputational models including individual anatomical constraints in order to predict physiological activity, behavior, and subjective feeling at the same time. Such models could also be used to describe abnormal cognitive processes and thus neuropsychiatric disorders.¹⁷

Connectomic studies comparing psychiatric patients with controls have already confirmed the early intuitions of Wernicke and Talairach. As a striking example, massive structural, functional, and effective dysconnectivities have been found in schizophrenia,^{35,67,74,90} leading some authors to propose a “disconnection hypothesis” of schizophrenia.^{40,41} According to this theory, schizophrenia would

result from an aberrant modulation of synaptic efficacy, leading to functional and effective dysconnectivity, and ultimately to structural dysconnectivity. Note that even if this hypothesis posits a ubiquitous mechanism, dysconnectivity is not necessarily homogeneous. Highly centralized and interconnected hub regions may be particularly affected in schizophrenia.⁸⁶ Closer to the topic of this paper, alterations of the connectome have been demonstrated in two of the main psychiatric pathologies in which psychosurgery is an option, namely obsessive-compulsive disorder^{4,43,68,69} and depression.^{42,57} When coupled with mathematical tools such as machine learning (which establishes predictive links between features of the observed data and clinical variables), the connectomic approach can go further than just a quantitative comparison of populations. It might trigger the beginning of a new era of psychiatry by providing biomarkers and tools for nonclinically based diagnostics, prediction of disease evolution, or therapeutic guidance.¹⁷

Toward Individually Targeted Psychosurgery

As far as treatments are concerned, normalization of the functional dysconnectivity has been observed following clinical improvement in a wide range of therapeutic interventions, from psychotherapy^{20,91} to pharmacological treatments.^{2,45,77} Some authors have even claimed that modulation of connectivity could mediate, rather than just reflect, therapeutic effect. This is particularly the case for neurostimulation techniques such as repetitive transcranial magnetic stimulation (rTMS)²¹ or ECT.^{1,12,66,92} For example, rTMS to the dorsolateral prefrontal cortex may be effective in depression through long-term plasticity induction, leading to a reduction of the hyperconnectivity of the default mode network and a restoration of connectivity in a frontoparietal network. Similarly, the effect of deep brain stimulation (DBS) is predicted by connectomics and may be mediated by white matter.^{36,48,58,84} Thus, Figuee et al. demonstrated that stimulation of the nucleus accumbens in obsessive-compulsive disorder normalized nucleus accumbens activity but also critically reduced its increased (functional) connectivity with the prefrontal cortex as well as frontal low-frequency oscillations during symptoms.³¹ Regarding depression, DBS targeting the subgenual cortex/subcallosal cingulate cortex (which is currently the most effective target) is mediated by its impact on white matter rather than by direct cortical activations.^{62,72} This target appears to be an important triple functional node by connecting the right and left prefrontal cortex through the anterior part of the corpus callosum, medial frontal cortex to the cingulate system through the cingulum, and linking the subcallosal cingulate cortex to the mesial frontal cortex, subcortical structures, and anterior thalamus through the uncinate fasciculus. Moreover, a recent pilot study used individual tractography maps to determine targets in a patient-specific way, opening up the use of individual connectome mapping to guide therapeutic intervention.⁷¹

In light of these recent findings, and close to the visionary proposition of Jean Talairach,⁸¹ the connectomic approach coupled with modern computational analyses

could help to define pathological network organization and identify the anatomy of crucial nodes that neurosurgeons should target. However, as impressive as they are, current rTMS/DBS interventions are outperformed by coarser stimulation such as ECT. A potential explanation lies in the diversity of symptoms in psychiatry: as a striking example, according to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*, 2 patients could be diagnosed with major depression without sharing any common symptoms. Such diversity is likely to result from diverse underlying mechanisms. In other terms, beyond common impairments, specific pathological networks could result in specific clinical dimensions, and thus constitute specific putative targets. Following the framework proposed by Talairach, targeted psychosurgery would suppose interrupting pathological networks to allow neuronal plasticity that would (hopefully) lead to postsurgical psychic recovery. Provided that mental disorders result from abnormal structural or functional wiring, such an intervention would require that one be able 1) to identify, at the individual level, the pathological network involved in a given patient's plasticity; 2) to use neurostimulation, such as DBS, to safely create a reversible and durable alteration, mimicking a lesion, in a network compatible with neuroplasticity; and 3) to predict which functional lesion would result in adapted neuronal plasticity and/or to guide neuronal plasticity to promote recovery.

As far as individual predictions are concerned, recent studies have provided encouraging results. For example, it is now possible to establish an individual functional connectivity profile, which when used as a “fingerprint” can accurately identify subjects from a large group.³² Moreover, as discussed above, structural connectivity and effective connectivity may be coupled with a computational description of behavior to infer (patho)physiological mechanisms underlying clinical features. However, an appealing challenge would be to characterize these mechanisms at the individual level and use them to guide therapeutic intervention (see Stephan et al. for a comprehensive review of the computational approach to neuroimaging-based single-subject inference⁸⁰). Such an approach would dissect the heterogeneity of psychiatric diseases through the definition of subgroups characterized by specific network impairments and thus provide the foundation for targeted surgery. Provided that such connectivity-based pathophysiology is available, it should be possible to use DBS to mimic a lesion and thus trigger targeted neuroplasticity. Nevertheless, neurosurgeons would have to ensure that neural plasticity leads to psychic improvement and not to worsened symptoms! Current neurocomputational approaches might already help to predict short-term reconfiguration following an acute lesion through examination of the effect of virtual lesions in simulated networks.⁷⁰ However, as demonstrated by the long-term effect of psychosurgery—in current procedures in which lesions are induced, outcomes are usually assessed 6 months and up to 2 years postoperatively—long-term plasticity is probably involved.⁴⁴ To our knowledge, only 1 paper used a computational approach to investigate such long-term change in structural connectivity (following psychosurgery in Parkinson's disease). In a striking seminal paper,

van Hartevelt et al. demonstrated that 6 months postoperatively, DBS induced structural and functional alterations toward a healthy network, thus confirming Talairach's intuition about targeted psychosurgery.⁸⁷ Finally, it might not be enough to predict in which direction neural plasticity will shift brain organization: one could also want to guide such reorganization toward improvement. It would be like a surgeon making a controlled wound heal by restoring physiological conditions (good vascular environment, treatment of local infection, ablation of fibrin, etc.) and orienting the healing process. This idea leads to the intriguing possibility, already evoked by Talairach, that psychosurgery may be coupled with psychotherapy, pharmacology, or even neurostimulation to promote efficient neural plasticity following intervention.

Conclusions

When Jean Talairach imagined precursory concepts for targeted psychosurgery, based on the rich possibilities of psycho-neuroplasticity, both the remarkable progress of pharmacology and the technical limits of neurosurgery made it impossible to put them into practice. Currently, this context has evolved, and psychosurgery is being revived; due to several failures in new drug development and decreased cost-effectiveness, the development of neuropharmacology is reaching a limit, and is no longer the priority for numerous pharmaceutical companies.^{47,53,63} Furthermore, responder rates remain limited in psychiatry, and 1 in 3 patients suffering from a depressive disorder—the most frequent pathology—remain insufficiently improved despite optimal tritherapy.⁷⁶ In addition, suicide rates have not improved in Europe and North America over the past 25 years. Psychosurgery could stretch the limits of neuropharmacology, as an alternative or a potentiator. Moreover, modern biomarkers and surgical progress give psychosurgery strong scientific support, helping to make it safer and more ethical in clinical practice.

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Disclosures

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Author Contributions

Conception and design: Bourdillon, Vinckier. Acquisition of data: Bourdillon, Vinckier. Analysis and interpretation of data: Bourdillon. Drafting the article: Bourdillon. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: Bourdillon. Study supervision: Bourdillon.

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