Incisionless transcranial MR-guided focused ultrasound functional neurosurgery

---

Thèse d'habilitation présentée à la Faculté des sciences et de médecine

de l'Université de Fribourg (Suisse)

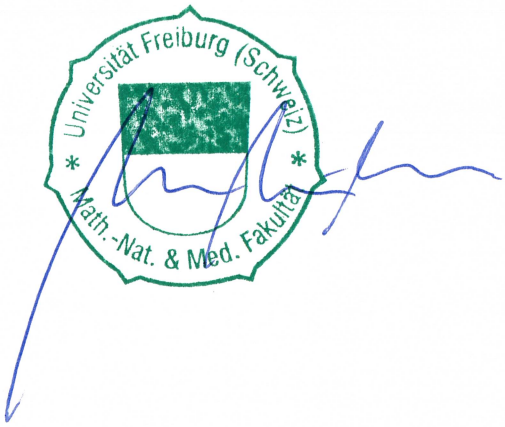
pour l'obtention de la venia legendi

par le **Dr. med. Marc Nicola Gallay**

d'Essertines-sur-Rolle (VD) et Mont-sur-Rolle (VD)

Rumisberg, 2024

Acceptée par la Faculté des sciences et de médecine de l'Université de Fribourg (Suisse)



Prof. Ulrich Ultes-Nitsche

Doyen

Faculté des sciences et de médecine

Université de Fribourg - Suisse

Fribourg, le 23 septembre 2024

Summary:

The first three sections of this work are dedicated to the application of Magnetic Resonance-guided focused ultrasound (MRgFUS) technology in stereotactic functional neurosurgery. The impetus behind these developments is to provide patients suffering from chronic and therapy-resistant neurological diseases, i.e., no longer, or insufficiently helped by drugs, with safer, more accurate and efficient stereotactic neurosurgical interventions to control their symptoms. The pathophysiological basis and choice of targets applied in the following studies were introduced from the early nineties onward by the group led by Professor Jeanmonod in Zürich and later in Solothurn, who also introduced the MRgFUS in functional neurosurgery in 2005[1–5]. The author had the opportunity to assist Dr. Anne Morel between 2005 and 2008 in her huge endeavor mapping the human thalamus, the basal ganglia, and the subthalamus in the stereotactic space. The latest version of her work was published as the "Atlas of the human Thalamus and Basal Ganglia" [6,7] and is nowadays used by many functional neurosurgeons around the world. After residency training in different neurosurgical clinics and national board examination, the author was recruited by the center for ultrasound functional neurosurgery in Solothurn opened in 2010 by Daniel Jeanmonod to develop and offer patients a better and broader access to the MRgFUS technology.

The accuracy and safety of the MRgFUS technique applied to Parkinson's disease (PD), essential tremor (ET), cerebellar tremor and neurogenic pain syndromes, all chronic and therapy-resistant were analyzed in the first section of this work. A total of 253 targets in 180 treatments were retrospectively assessed for accuracy of realized lesions as well as side-effects. This study was able to demonstrate a higher targeting accuracy thanks to the absence of brain shift and a lower side-effect profile than techniques requiring actual mechanical cerebral penetration. The absence of hemorrhagic events in this large series was particularly reassuring after the report of an intracerebral bleeding in the first study using the MRgFUS in functional neurosurgery[2].

The second section is devoted to the neurosurgical treatment of chronic and therapy-resistant Parkinson's disease and was the subject of four papers between 2019 and 2021[8–11]. Our contribution follows the first experience with the MRgFUS in PD reported by Magara et al. in 2014[5]. The authors of this study performed a unilateral pallidothalamic tractotomy (PTT) with the help of the MRgFUS in 13 patients. The PTT is in fact an "old" surgical target theorized and applied in the sixties by different international groups (mainly in the USA and

Germany[12,13]) and "re-actualized" by the Jeanmonod group in the nineties[14,15]. Symptom recurrences or only partial symptom control from this early experience with the MRgFUS led us to develop a stereotactic protocol, after histological re-analysis of the anatomy of the subthalamus and its interindividual variations. This optimized target coverage[8] was validated in 31 interventions from a radiological point of view[9] and subsequently in two further clinical articles[10,11]. This modified approach was applied without interruption since the beginning of 2017, the first 56 treatments of which were analyzed and published in 2020[10]. PD is a disease that in most cases involves both cerebral hemispheres. Nevertheless, there have been longstanding caveats about bilateral approaches due to the inevitable risks of procedure. However, our group's demonstration of an improved lesioning accuracy, a reduced bleeding risk and an absence of procedure-associated infections, set the basis for our investigation of bilateral MRgFUS interventions. The results of bilateral PTT were analyzed in two of our contributions[10,11]. All interventions performed were monitored by the Federal Office of Public Health of Switzerland in the context of a registry run by this office.

The third section is devoted to the surgery of ET using MRgFUS to perform cerebellothalamic tractotomies (CTT), mostly unilaterally, but also bilaterally in a few cases. There is sound histological evidence that the so-called posterior subthalamic area (PSA) also named prelemniscal radiation by Hassler or posterior zona incerta includes in fact the cerebellothalamic (or dentato-thalamic) fibre tract on its way to the posterior part of the thalamic ventral lateral nucleus (VLp). Our first series of 2016 was the first to include patients operated for chronic therapy-resistant ET with the MRgFUS CTT[16]. This first series was completed by a second work [17] in which refinements of the targeting technique were described, leading to improved clinical results.

The results of a reappraisal of the cytoarchitecture of the insula of Reil, an anatomical structure strongly involved in the pathophysiology of neurogenic pain, first in the monkey (Macaca mulatta and fascicularis) using multiarchitectonic criteria and later in the human, are presented in the fourth section. Our study of the human insula included correlations between histological sections and high-resolution postmortem stereotactic MR images.

General introduction

Functional neurosurgery is a field of neurosurgery involved in the restoration of neurological function. It is neuroanatomy and neurophysiology applied to the human being. Neurosurgeon Russel Meyers demonstrated in the late thirties that basal ganglia surgery could be performed without impairing consciousness [18]. This first type of surgical of intervention on the basal ganglia represented a major paradigm shift in the battle against chronic neurological diseases, as for the first time, neurological improvements i.e., reduction of symptoms did not need to come at the price of new neurological deficits as had obviously been the case with cortical ablations, cordotomies or mensencephalotomies. At this stage, "open" surgical approaches, i.e., via opening of the skull, were still mandatory.

The first apparatus conceived to perform human stereotactic neurosurgery published in the literature was developed by Spiegel and Wycis [19] as a direct modification of the Horsley-Clarke animal apparatus described in the first decade of the twentieth century [20]. Surgical stereotaxis is based on the calculation of precise spatial relationships between any structure found deep within the brain and several points or landmarks that serve as intracerebral or cranial reference structures. The first known "stereotaxic" device was developed by Zernov at the University of Moscow in 1889 [21,22]. The spelling "stereotaxic" (Greek stereo and taxis = three dimensional arrangement) was changed to "stereotactic" (three dimensional/touch) in 1973 only [23]. Jean Talairach, a French neurosurgeon, is credited for the use of the anterior and posterior commissures, as references for a brain coordinates system (1952).

The impetus for the development of functional neurosurgery is best understood must be placed in the context preceding modern pharmacological discoveries. At that time, patients with chronic neurological disorders could only resort to neurosurgical interventions. The catastrophic breakout of Encephalitis lethargica (Von Economo's disease) in 1916 is a tragic example of this. It left thousands of, often young, postencephalitic patients with neurological sequelae and without treatment. It was estimated that as many as 60% of those post-encephalitic patients who survived the acute phase developed a parkinsonism (50% with a latency period of less than 5 years). The average age of onset of postencephalitic parkinsonism was approximately 27 years [24,25]. Drug treatments, L-DOPA for example came to be administered as a regular treatment in Parkinson's disease (PD) only at the end of the sixties [26].

The worldwide spread of the stereotactic technique took place from the late forties onward and procedures were intensively developed to tackle various chronic neurological diseases such as neurogenic pain syndromes after amputations or nerve damage, movement disorders (e.g. Parkinson's disease, various tremors or dystonia), epilepsy or neuropsychiatric disorders [12,13,19,21,27–38,38–55]. During this period, most functional neurosurgical groups developed a stereotactic apparatus of their own design.

Lesioning techniques

The main risks of any intervention within the brain were (and still are) bleeding, infection, and neurological side-effects via encroachment (injury) on neighboring structures. In comparison to open procedures, the development of stereotactic techniques in functional neurosurgery led to a drop in these perioperative risks. It brought a tremendous decrease in operative mortality which nevertheless still reached 2.5% in the 1960s (compared to the 10-15% observed with open techniques [56]). The surgical morbidity of these early series remains difficult to translate into modern reporting standards. The lesioning techniques developed during those pioneering years included cryosurgery, anodal electrolysis, thermocoagulation, the use of radioactive isotopes, chemical and mechanical methods [21]. In the 1990s, the most common lesioning technique was radiofrequency (RF) thermocoagulation. Clinical results, although lacking modern criteria for reporting were nevertheless impressive in the context of limited imaging modalities for guidance; indeed, ventriculography and plain x-rays were used to reach deep-seated targets within the brain. These relatively favourable results were probably influenced by an overall younger patient age as compared to nowadays cohorts (early stereotactic operations were seldom performed for patients over 70 years). Additionally current patients tend to be therapy-resistant, whereas drug resistance was not a surgical criterion at the time seeing that such drugs were not available.

Historically, the uncertainty during radiofrequency (RF) electrode insertion related to brain shift with consequent neurological deficits produced by misplaced thermolesions has been of great importance in the development of deep brain stimulation (DBS) techniques. Numerous reports have described clinical results of DBS in Parkinson's disease and essential tremor, accompanied however with significant procedure-related risks. The main procedure-related side-effects of DBS are bleeding and infection as well as hardware-related complications requiring a return to the operating room for electrode repositioning or hardware replacement. A hardware removal or revision rate of up to 34% was reported by Rolston [57] and an 8.4 %

hardware-related complication rate per electrode-year was reported by Oh and collaborators [58].

The advent of radiosurgery in the sixties [59] and later the Magnetic Resonance guided Focused Ultrasound (MRgFUS) technique [1] were decisive steps toward a reduction in perioperative risks. These techniques bypassed the need for cutting into skin and bone and did not require any tract penetration to perform small lesioning volumes deep inside the brain.

The Gamma Knife technique brought about interesting perspectives for safer and less invasive approaches in more fragile patients but was eventually found wider application in the neuro-oncological setting rather than in functional neurosurgery. Gamma Knife thalamotomy has been shown to achieve significant reductions in tremor scores in the long term; the permanent neurological deficits generated were partly due to unpredictable excessive radiation reactions [59–77] which may develop over months or even years after the procedure[78]. In Friehs et al.[79], these reactions did do not occur before 6-12 months after radiosurgical treatment.

The main advantages of MRgFUS over radiosurgery, aside its use of non-ionizing energy, are the direct control over the thermal lesioning process provided by on-line MR-thermometry, the reversibility of the procedure at low temperatures, and direct intraoperative clinical feedback during the lesioning process. In contrast to MRgFUS or RF thermal lesioning, thalamic lesions produced with Gamma Knife only gradually develop over the first 3 months and tend to reach their peak size at 6-12 months, subsequently declining in size[80].

MR-guided focused ultrasound (MRgFUS) functional neurosurgery

Focused ultrasound is thought to affect tissues through a variety of mechanisms, including cavitation, mechanical forces and direct heating[81]. The latter has been exploited in the development of the MRgFUS technique applied to functional neurosurgery. Selective heating by tissue absorption of ultrasonic energy can be controlled under real-time MR-thermometry to perform small and accurate therapeutic lesions deep within the brain without the need to open the skull and penetrate the brain. The temperature increase in the tissue depends on the intensity of ultrasound energy and the acoustic absorption coefficient of the tissue. Already in the 1950s, the Fry brothers developed a first prototype of piezoelectric transducers and demonstrated that focused ultrasound could be used after craniotomy for deep-seated targets

inside the brain of primates [82–85]. This early prototype rapidly found applications in the treatment of various brain pathologies such as brain tumors or PD in a cooperation with neurosurgeon Russel Meyers [86,87]. The Swedish neurosurgeon Lindström was another early pioneers of focused ultrasound-assisted neurosurgical procedures [88]. However, the need for a craniotomy and the lack of a reliable means of real-time monitoring instead led the neurosurgeon Lars Leksell to develop the Gamma Knife technique in the late 1960s.

The development of phased-array ultrasound transducers corrected for phase aberrations (distortion of the phase of the transmitted ultrasound wave due to variations in the speed of sound within the tissues) and use of a hemispheric transducer design in the 1990s allowed to focus the ultrasound beams through the skull, obviating the need for a craniotomy. The other major revolution in the development of modern focused ultrasound neurosurgery came with improvements in MR technology. MR was at last able to provide precise intraoperative guidance as well as real-time thermometry with an accuracy inside the targeted brain area of $\leq 1°C$ at 3.0 Tesla field strength [89,90]. The first commercially available MRgFUS neurosurgical unit was marketed by the company Insightec Ltd. (Haifa, Israel).

Previously, challenging targets located deep within the brain became the best treatable with MRgFUS, thanks to optimal ultrasound focusing at the center of the Insightec hemispherical transducer. Conversely, brain regions located closer to the skull are more challenging for MRgFUS due to the difficulty in focusing sufficient ultrasound energy on the target.

The first MRgFUS trial in functional neurosurgery targeted neurogenic pain. Its results were published in 2009 [1] and 2012 [2]. Since 2013, clinical trials have investigated the application of MRgFUS in essential tremor [16,17,91–108], obsessive compulsive disorder [109], Parkinson's disease [5,8–11,110–116] and dystonia[117–119]. The medial thalamus (central lateral nucleus) was the first neuroanatomical structure to be targeted by the MRgFUS system[1,2]. Later followed the motor thalamus[92,120], the posteroventral internal pallidum[112], the anterior capsule[109], the pallido-[5] and cerebellothalamic[16] tracts and finally the subthalamic nucleus[111].

The MRgFUS is a surgical procedure performed without a skin incision, without drilling of the bone and without penetration of the brain. Yet, as we have discussed above, it is by no means a "noninvasive" procedure. We have therefore favoured the term "incisionless" in our publications.

Advantages of the MRgFUS

MRgFUS currently offers the possibility to heat cerebral tissue by delivering minute ellipsoidal (1.5-2.5 mm for the short and ~3 mm for the long diameter) thermal doses both accurately and under the control of MR thermography. Accuracy of targeting is confirmed at temperatures of tissue below lesioning threshold before committing to an irreversible lesion of the target structure. No narcosis or sedation is required. In contrast to Gamma Knife, no ionizing energy is used. This avoids the risk of unpredictable tissue reactions months after treatment. The absence of penetration-related brain shift avoids the risk of placing the thermolesion off-target. Whilst bleeding risk is reported to be around 2% (symptomatic bleedings) with DBS[121], it is much lower with MRgFUS (0 bleeding events in > 600 targets performed at our institution and 1 recorded bleed worldwide in several thousand interventions). As expected with an incisionless technique, infections do not represent a procedural risk; In contrast, the prevalence of infection following DBS procedures is estimated at 5.0%[122] at least.

Present (2022) limitations of the MRgFUS

To ensure a high level of accuracy in lesioning, a stereotactic frame needs to be placed around the patient's head. Its placement is performed under local anesthesia but can still involve some pain due to the pressure of the four fixation pins on the skull. The procedure, even if performed by a routinized team lasts between 2 and 4 hours according to which and the number of targets chosen. The skull is a significant barrier to ultrasound transmission. This can prevent therapeutic temperatures to be reached. The percentage of patients with "unfavorable" skulls varies greatly between ethnic groups. In our experience over more than 500 patients, it concerns less than 1-2 %, but in the Japanese population this estimation will be around 20% (Dr. Shiro Horisawa, personal communication).The hemispherical mid-frequency (650 kHz) used for thermal ablations in functional neurosurgery has a limited treatment envelope (around 3 cm radius around the mid-commissural point). Due to incident angle issues, the efficacy of sonications decreases for targets outside the center of the brain. In terms of efficacy on treating symptoms, the results will depend on the ability of the neurosurgeon and his team to target properly the desired neuronal structure with the optimal lesion (size and location), provided of course a careful patient selection. The lack of intraoperative electrophysiological control can be viewed also as a limitation, especially in structures lacking clear anatomical boundaries (e.g., the motor thalamus).

The primary handling of the MRgFUS system is fairly simple but optimal targeting and optimization of target coverage requires a long learning curve and experience in lesional functional neurosurgery. The dominance of DBS in the field of functional neurosurgery, has led to a lack of training in the neurosurgical community for placing safe lesions inside the human brain. This lack of training presents in our opinion a limitation to a safe rapid expansion of the MRgFUS technique worldwide.

In 2022, more than 100 centers worldwide are equipped with a MRgFUS system dedicated to intracranial interventions. Most of them are university clinics, with some notable exceptions. FDA approval in the United States of America was granted so far only for ET and PD. Depression, neuropathic pain and obsessive-compulsive disorder are approved in some countries but not in the USA. ET, PD and Neuropathic/Neurogenic pain were approved by the Federal Office of Public Health of Switzerland and monitored since 2015 in the context of a registry controlled by this office. In 2022, of those three indications, only Neuropathic Pain was still under registry, ET and PD having been definitely integrated in the basic insurance coverage for all Swiss residents.

Besides the placement of minute and accurate therapeutic lesions deep inside the brain, the MRgFUS offers further promising therapeutic approaches (detailed in an excellent review by Prada et al. [123]). Thermal ablations were tried to treat brain tumors in the early phase of development of MRgFUS but were discontinued early due to complications[124,125]. One case report about MRgFUS in a Glioblastoma multiforme did not show any complication, but no follow-up of the patient was provided[126]. An alternative approach using the FUS against brain tumors or for ablative procedures in epilepsy surgery could be histotripsy. Histotripsy is a non-ionizing and non-thermal, cavitation mediated mechanical destruction of tissue using focused ultrasounds delivered from outside the body. Is has been already investigated in neurological diseases in preclinical studies but so far human clinical trials were restricted to benign prostate hyperplasia, liver cancer and calcified valvular stenosis (for review[127]).

Contrast agents (e.g. intravascular microbubbles) can enhance tissue ablation exploiting controlled cavitations to achieve larger thermal lesions in tumors[128]. The blood-brain-barrier (BBB) is the principal obstacle to deliver chemotherapy inside of brain tumors. Through temporary opening of the blood brain barrier, a targeted drug delivery could help treating not only brain tumors but also neurological disorders[129,130]. Besides the BBB, the electrostatically

charged extracellular matrix and glial-lymphatic system represents a dense structure which limits the diffusion of therapeutic agents. Nanoparticles were engineered with dense poly(ethylene glycol) coating and applied in combination to FUS to overcome this obstacle[131] (preclinical study). Reversible cell membrane poration with FUS, called sonoporation could be used in vitro for incorporation in tumor cells of heat-activated chemotherapy, gene therapy, nanoparticles, and liposomes avoiding the systemic effects of those therapies[132,133]. Hyperthermia is known to induce changes in tumor milieu that could potentially enhance tumor responsiveness to radiation treatment (increase blood flow and consequently delivery of oxygen and trophic molecules thus enhancing tumor metabolic activities)[123]. Sensitized tumors could require a lower dose of radiation to be effective[134]. FUS can induce a sensitization to radiotherapy[135]. In a similar way, FUS could enhance the sensitivity to chemotherapy thanks to several mechanisms.

Another way to apply the FUS is to influence immune response against a tumor (immunomodulation) through various mechanisms, e.g. overexpression of heat shock proteins induced by FUS thermal ablation[136].

The concept of sonodynamic therapy is also very promising. Sonosensitizer molecules, e.g. 5-aminolevulinic acid (5-ALA) are activated with the help of the FUS to obtain necrosis and apoptosis in the targeted area (tumor)[137].

In the area of cerebrovascular diseases, sonolysis has been proposed not only for mechanical clot lysis in occluded vessels but also for clot hemolysis in intraparenchymal hemorrhages[138].

Contribution of the Author to the field of MRgFUS and Anatomy of the Insula of Reil

The Author was fortunate to meet and start working for Drs Morel and Jeanmonod during his medical school years. He could join in 2005 the laboratory for stereotaxic functional neurosurgery in Zürich. None less than Professors Krayenbühl, Yasargil and Siegfried preceded Professor Jeanmonod in this famous lab. The same Daniel Jeanmonod, who never stopped improving and developing new functional neurosurgical approaches to chronic and therapy-resistant disorders with the radiofrequency was the first to introduce the MRgFUS technology in functional neurosurgery with his seminal studies on MRgFUS CLT against neuropathic pain along his college radiologist Professor Ernst Martin.

The author had the opportunity to assist Dr. Anne Morel between 2005 and 2008 in her huge endeavor mapping the human thalamus, the basal ganglia, and the subthalamus in the stereotactic space. The latest version of her work was published as the "Atlas of the human Thalamus and Basal Ganglia" [6,7] and is nowadays used by many functional neurosurgeons around the world. The next topic of research was the Insula of Reil, an especially important but often neglected cortical area, whose importance in neuropathic pain is no longer to be demonstrated. The insula was studied first in the smaller brain of the macaque monkey for histological and immunohistochemical parcellation and later in human with the adjunction of postmortem MR images prior histological processing. These studies on the Insula provided a framework for future investigations on the functional (electrophysiological) and connectional aspects of the insula in primates species, including humans (epilepsy surgery). The produced template of the human insula was though to help at improving localization into in vivo MR standard and functional imaging and clinical applications.

Since joining the center of functional ultrasound neurosurgery, the impetus was to provide patients suffering from chronic and therapy-resistant neurological diseases, i.e., no longer, or insufficiently helped by drugs, with safer, more accurate and efficient stereotactic neurosurgical interventions to control their symptoms. The pathophysiological basis and choice of targets applied in the following studies were introduced from the early nineties onward by the group led by Professor Jeanmonod in Zürich and later in Solothurn.

The first contribution of the Author to the field of MRgFUS was a retrospective analysis of uni- and a few bilateral MRgFUS CTT cases operated between 2011 and 2015. With growing numbers of interventions performed, the next step had been to analyze the accuracy and safety of the MRgFUS system in a large cohort of patients (180 treatments). The first data on MRgFUS PTT had been published by Magara et al in 2014. The results were promising, but follow-ups showed to many recurrences and only partial symptom control. This motivated a thorough histological re-analysis of previously only partially published material used by Dr Morel to publish the second version of her stereotactic atlas of the human thalamus and basal ganglia. In superimposing the pallidothalamic tract of cases with different anterior-posterior commissure lengths, adjusted on the mammillothalamic tract, a structure always visible on myelin-stained sections we could clearly identify the need to expand the antero-posterior but also the medio-lateral extension of the target to integrate the interindividual variability. The proposed model was and still is very conservative in the vicinity to the mammillothalamic tract and internal capsule for obvious safety reasons. This is a weakness in cases of

exceptionally large subthalamic regions (in the ml but also ap directions). A way to further improve targeting beyond a histological model, would be to be able to rely more on preoperative MR images (for example 7 Tesla high resolution sequences) to correct the medio-lateral and antero-posterior extension of the target.

The model of the target proposed was applied first on 31 interventions and correlation data on thermal doses applied and MR images were published in a second contribution on PD. Along the histological model, a new protocol using sonications of shortest duration possible and corresponding high power to reach 240 CEM in each of the 5 to 7 preplanned target sub-units was proposed. These technical modifications were integrated in the clinical routine and clinical data were published first on 51 patients and later 10 bilateral MRgFUS PTT cases with 1-year follow-up after operation of the second brain hemisphere.

The original CTT target was also revisited from a histological viewpoint and a new target protocol proposed following the same line of thoughts as for the PTT target. In the case of CTT, a new reference point was chosen for the model of the target. This reference point (the middle of the red nucleus, cut 3 mm below the intercommissural plane) had then to be identified on planning images and reported intraoperatively on lower resolution MR-images (body-coil) along anterior and posterior commissures. This led to an improvement of postoperative results from an average of 70% tremor control at 1-year follow-up to ~90% in the first series of 10 patients. In 2022, tremor control as rated by the patients for the operated body-side was 87% after more than 60 interventions at 1-year follow-up (publication in preparation). Longer follow-ups and bilateral treatments show the same amount of tremor control.

Section one: Safety and Accuracy of MRgFUS

Gallay MN, Moser D, Jeanmonod D: Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments. Journal of Neurosurgery 1:1–10, 2018

Open functional neurosurgical interventions, performed over 80 years ago, carried a high risk. Mortality rates were high (12-16%) and symptom improvement was as low as 19% in early series[45]. The introduction of the stereotactic technique by Spiegel and Wycis[19] in the 1940s resulted in a decrease in mortality and morbidity, as well as a significant increase in postoperative symptom improvement[33,139]. This led to the early global development of functional neurosurgery. With the improvement of image guidance, the accuracy of therapeutic lesioning inside the brain improved, leading to more effective treatments of symptoms in the following decades.

The uncertainty caused by brain shift during electrode insertion into the brain and the subsequent neurological deficits produced by misplaced lesions played a major role in the development of deep brain stimulation (DBS) techniques in the early 1990s. The DBS technique eliminated the risk of lesioning the wrong neuroanatomical structure, but it has been associated with significant procedure-related risks. The main procedure-related side effects of DBS include bleeding (with an overall incidence in functional neurosurgery of 5.0 % and 2.1 % being symptomatic and 1.1 % resulting in permanent deficits or death)[121], infection (estimated prevalence of 5.0 %[122], with probable great variations between institutions), and hardware-related issues (with a removal or revision rate of up to 34% as reported by Rolston et al.[57], and an 8.4% hardware-related complication rate per electrode-year reported by Oh et al.[58]). A review of the literature by Hamani et al.(2006)[140] (922 patients, in 10 articles) found infections in 6.1%, migration or misplacement of leads in 5.1%, lead fractures in 5.0%, and skin erosion in 1.3 % of patients. Burchiel et al. (2013)[141] found a mean vector error in placement of DBS electrodes of 1.59±1.11 mm and mean deviation off trajectory of 1.24±0.87 mm. These data are in line with a previous report on accuracy of radiofrequency lesioning[142]. Starr et al.[143] found a mean absolute tip error of 2.2±0.9 mm in the placement of 53 DBS electrodes into the subthalamic nucleus (STN) using interventional MR (iMR) imaging-guided navigation, which was significantly smaller than the error for electrodes implanted using traditional frame-based stereotaxy (3.1±1.4 mm).

In his 1989 monograph[21], Dr. Kandel described the requirements an ideal technique for lesioning stereotactic operations: 1) the size of the focus should be directly related to the instrument of destruction, 2) we should have the possibility of controlling the size of the lesion and in particular of terminating destruction immediately on appearance of symptoms of involvement of adjacent structures of the brain, 3) minimal reaction of adjacent cerebral tissue to the lesion, 4) absence of general reactions or damage to the brain, 5) almost total exclusion of the danger of vascular injury, 6) possibility of reversing the inactivation of a structure before its destruction and 7) procedures for destruction of cerebral tissue that are not unduly lengthy and that are convenient and simple.

In our opinion, MRgFUS is the closest technique to meet all these requirements described by Dr. Kandel. The target size can be reasonably well predicted[9,144,145], the patient is awake and sonications can be stopped at any time in case of side-effects. There have been no reports of significant surrounding edema after the procedure, no general reactions of the brain, and no bleedings (over more than 650 targets performed in our institution and many thousands of cases performed worldwide) since the installation of cavitation detectors. Low power sonications at reversible temperature thresholds are used to control the accuracy of lesioning, and the mean duration of interventions has decreased from 5.6±1.8 hours for the first 450 to 2.7±0.4 hours for the last 100 treatments at our institution.

To quote Kandel[21] again, “Stereotaxis, first of all requires maximal accuracy. The success of any stereotactic operation depends on many factors but primarily on the accurate localization of the subcortical target. If the calculations are inaccurate, and the stereotactic instrument deviates from the target point only 2-3 mm, or if there are other technical defects, not only will the result be imperfect but serious complications may arise.”

In the period between the publication of the first MRgFUS trial in 2009[1] and 2017, around 200 treatments were reported. However, due to the small number of patients in each reported series, no reliable profile of procedure-related risks could be determined. In our study, “Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments”[146], we analyzed consecutive treatments performed using MRgFUS technology between April 2011 and November 2016. The treatments were carried out for patients with chronic and therapy-resistant idiopathic Parkinson’s disease, Essential tremor, neuropathic pain, and cerebellar tremor. Monitoring for side-effects continued for at least three months after the procedures.

The surgical targets were identified using the stereotactic atlas of the human thalamus and basal ganglia of Morel and included the pallidothalamic tract (n=105), the cerebello-thalamic tract (n=50), the central lateral nucleus (n=84), the centre médian nucleus (n=12) and the globus pallidus (n=2). The accuracy of lesioning was evaluated based on postoperative MR

The mean accuracy of the 234 thermal lesions measured was 0.32±0.29 mm, 0.29±0.28 and 0.44±0.39 mm in the mediolateral, anteroposterior and dorsoventral dimensions, respectively. The mean 3D accuracy (Euclidian vector) was 0.73±0.39 mm. Nine (3.8%) error measurements were ≥ 1.5 mm in the mediolateral, 5 (2.1%) in the anteroposterior, and 19 (7.9%) in the dorsoventral dimensions. 37,6% of patients experience brief (less than 10 seconds) but intensive pain, localized frontally. There was no long-lasting headache after the procedure. Procedure-related sides-effects included 2 cases of benign subcutaneous swelling on the forehead that resolved within a week. Three side-effects were classified as effects on neighboring structures due to the extension of the thermal lesion beyond the target, causing slight hypesthesia on the lower lip and slight reduction of gustation in one patient. In a second case, paresthesia around the mouth on the left and on the left hand (without somatosensory deficits) appeared on day 2 after Centre Médian thalamotomy and lasted a few weeks. One decompensation of mnestic functions was seen in one parkinsonian patient, possibly related to thermal effect or edema-related compression on the mammillothalamic tract. There was no bleeding, and as expected from an incisionless technique, no infections.

Our study showed that MRgFUS has a higher targeting accuracy and a lower risk of side effects compared to brain penetration techniques like radiofrequency and deep brain stimulation. Clinical effectiveness, however, depends on proper target and patient selection, and proper thermolesional coverage of the target.

Since our publication in 2018, a safety analysis by Fishman[147] of MRgFUS thalamotomy in 186 patients from 5 studies confirmed its safety, with only 1.6 % of patients experiencing serious adverse events, including no intracerebral hemorrhages or infections.

To the best of our knowledge, no large study has re-analyzed the accuracy of MRgFUS since our publication of 2018.

Section two: Incisionless MR-guided focused ultrasound for chronic therapy-resistant Parkinson's disease

Gallay MN, Moser D, Federau C, Jeanmonod D: Anatomical and Technical Reappraisal of the Pallidothalamic Tractotomy with the Incisionless Transcranial MR-Guided Focused Ultrasound. A Technical Note. Front Surg 6:**2019**

Gallay MN, Moser D, Federau C and Jeanmonod D: Radiological and thermal dose correlations in pallidothalamic tractotomy with MRgFUS. Front Surg:**2019**

Gallay MN, Moser D, Rossi F, Magara AE, Strasser M, Bühler R, et al: MRgFUS Pallidothalamic Tractotomy for Chronic Therapy-Resistant Parkinson's Disease in 51 Consecutive Patients: Single Center Experience. Front Surg 6:**2020**

Gallay MN, Moser D, Haufler F, Jeanmonod D. **(2021)** Bilateral MRgFUS pallidothalamic tractotomy for Parkinson's disease with one year follow-up. Front Neurol: **2021**

Parkinson's disease (PD) is a complex neurological disorder characterized by the early death of dopaminergic neurons in the substantia nigra pars compacta. The resultant dopamine deficiency within the basal ganglia leads to a movement disorder produced by overactivity of the thalamocortical system. The disorder is characterized by classic parkinsonian motor symptoms, such as tremors, rigidity, and hypobradykinesia. In addition to these motor symptoms, PD is also associated with numerous non-motor symptoms, some of which can occur more than a decade before the onset of motor dysfunction[148]. The prevalence of PD for all ages in Europe ranges from 66 to 1500 per 100,000 people, and its incidence varies from 5 to 26 per 100,000 person-years[149].

Organization of the basal ganglia

The sources for this short introduction to the organization of the basal ganglia were mainly three standard textbooks[150–152]. The basal ganglia are nuclear complexes located in the midbrain and cerebrum that play a critical role in the integration of various functions, such as motor activity. They integrate and process afferent inputs from the cerebral cortex and send the modified signals to the thalamus, which after further alteration relays the output back to specific areas of the cerebral cortex. This group of nuclei also is of great importance in mechanisms involving emotional and cognitive behaviors. The basal ganglia are considered to include the corpus striatum, the subthalamic nucleus, the ventral tegmental area (VTA), the substantia nigra pars compacta (SNc) and reticulata (SNr) and the pedunculopontine nucleus (PPN). The corpus striatum is divided in striatum (neostriatum) and globus pallidus (GP) (pallidum, paleostriatum). The striatum itself is further divided into the putamen (which constitutes about 55% of the volume) and the caudate nucleus (about 35%), which together form the dorsal striatum. The GP is divided into medial or internal (GPm or GPi) and lateral or external (GPl or GPe) segments, as well as the ventral pallidum. The substantia nigra consists of two parts, known as the pars reticularis and pars compacta, which differ in neuronal densities and hence have distinct connectivity and neurotransmitters. The putamen and globus pallidus are somatotopically organized.

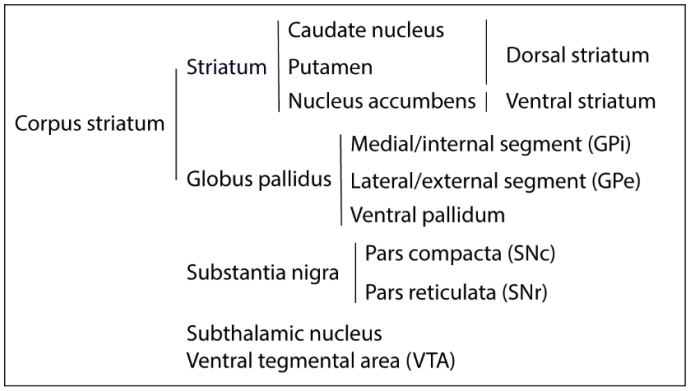


Figure 1: Basal ganglia and related centers

Around 90% of neurons within the striatum are GABAergic inhibitory projection neurons that form two functional subgroups expressing different receptors. One subgroup projects to the GPi and the SNr, constituting what is called the direct pathway that facilitates activity. The other subgroup projects to the GPe, which then projects to the STN, and is called the indirect pathway that elicits inhibition. Both groups of projection neurons receive excitatory glutaminergic cortical inputs, as well as modulatory dopaminergic inputs from the SNc.

While different receptors exist on striatal projection neurons, dopaminergic receptors receive their input from nigrostriatal (SNc) afferents. Dopamine receptors on direct pathway projection neurons are referred to as D1-type, and neurons of the indirect pathway are called D2-type. Dopaminergic input is excitatory for D1-neurons, promoting the direct pathway, and inhibitory for the D2-neurons of the indirect inhibitory pathway. A healthy substantia nigra is tonically active, favoring activity in the direct pathway. All projections from the cerebral cortex arise from pyramidal cells and are excitatory (glutaminergic). Those from the striatum and from both segments of the globus pallidus (GPi, GPe and ventral pallidum) arise from inhibitory GABAergic neurons.

The GPi and SNr represent the output nuclei of the basal ganglia. The output from the GPi projects through the ansa lenticularis and fasciculus lenticularis. Both tracts merge into the thalamic fasciculus before reaching the thalamus. These are tonically active inhibitory GABAergic neurons that project to the thalamus and brainstem nuclei. Their activity is modified by the direct and indirect pathways. The direct and indirect pathways main role is to reinforce a chosen motor act, inhibit those that are unchosen and thereby ensure the activation of a specific motor program that is required. There is one additional projection from the cerebral cortex directly to the subthalamic nucleus, the hyperdirect pathway, which allows the cerebral cortex to bypass the striatum and directly activate this nucleus to inhibit motor activity.

There are at least four circuits that traverse the basal ganglia and return to the cortex. The basic core circuit comprises cerebral cortex, striatum, globus pallidus, thalamus and cerebral cortex again. The processed information is then transmitted via upper motoneuron pathways to the lower motoneurons. A feedback loop goes back to the striatum via thalamostriate fibers from the intralaminar nuclei. The general core circuit serves as a template for the other parallel loops that convey functionally distinct information from different cortical regions. These include: 1) a motor loop for voluntary and learned movements, 2) a cognitive loop for planning and motor intentions, 3) a limbic loop for emotional aspects of movement and 4) an oculomotor loop concerned with voluntary eye movements and saccades.

While the basal ganglia are not typically responsible for initiating movements, they play a crucial role in all movements, regardless of speed. Their main function is to modulate the strength of muscle contractions and, in conjunction with the supplementary motor cortex

(SMA), to organize the necessary sequences of cell columns in the motor cortex. This activity occurs after the corticospinal tract has been activated by premotor areas.

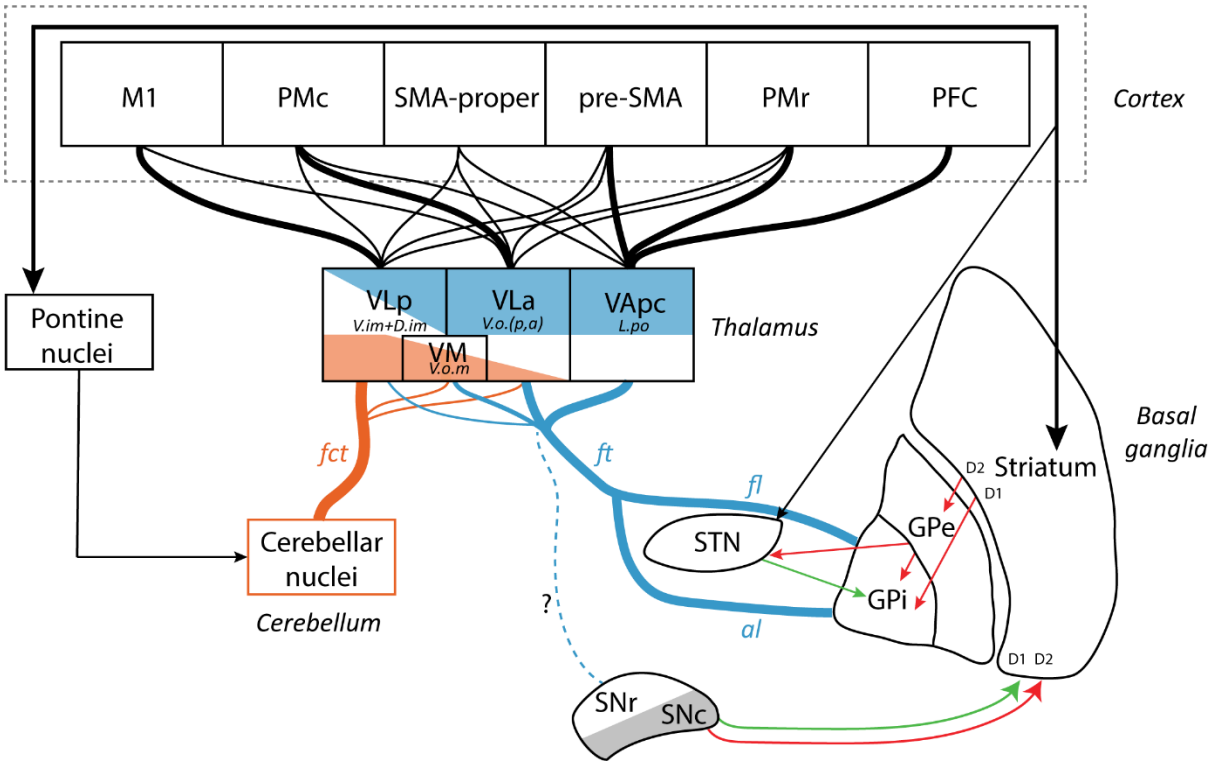


Figure 2: Modified from Gallay et al. 2008[6]. Simplified diagram of the cortico-cerebello-thalamocortical and cortico-basal ganglia-thalamocortical circuitry based on data derived from tracing studies in monkeys. The cerebellar nuclei project to the motor thalamus via the fasciculus cerebello-thalamicus (fct), with primary target in the ventral lateral posterior nucleus (VLp), but also in ventral lateral anterior nucleus (VLa) and ventral medial nucleus (VM) (projections to medial thalamic nuclei are not included in the schema). Efferent connections of the GPi to the thalamus course through the ansa lenticularis (al) and the fasciculus lenticularis (fl), and the two fibre bulks merge to form the fasciculus thalamicus (ft) which projects primarily to the VLa, ventral anterior nucleus parvocellular division (VApc), and VM nuclei, with only minor projections to the VLp (projections to the intralaminar nuclei are not shown). Equivalent Hassler's nomenclature for thalamic nuclei is also indicated. Dorsomedial intermediate medial (D.im), Ventral intermediate medial (V.im), ventral oral anterior or posterior (V.o.a,p) and lateropolaris (L.po). Connections to the thalamus and cortex are represented with different thicknesses according to their relative density and by different gradients in the thalamus. The two major motor pathways are also represented by different colors for clarity. The connections of the SNr are not depicted but they are thought to be identical of the GPi. In the basal ganglia, Inhibitory inputs are represented by red arrows, excitatory inputs by green arrows. Dopaminergic receptors typ 1 (D1) and dopaminergic receptors typ 2 (D2).

Parkinson's disease models

The following figure shows the classical model of PD, which follows the progressive failure of dopamine production by the SNc as precipitating cause of PD. According to this model, the essential pathophysiological characteristic of the parkinsonian state is increased neuronal activity in the GPi/SNr output nuclei, leading to excessive inhibition of thalamocortical and brainstem motor systems. The model predicts that reduced activation of dopamine receptors results in reduced inhibition of neurons of the indirect pathway and decreased excitation of neurons of the indirect pathway. Reduced inhibition from the indirect pathway leads to overinhibition of the GPe (-), disinhibition of the STN (+), and increased excitation of the GPi/SNr neurons (+++), whereas decreased activation from the direct pathway causes a reduction in inhibitory influence on the GPi/SNr[153].

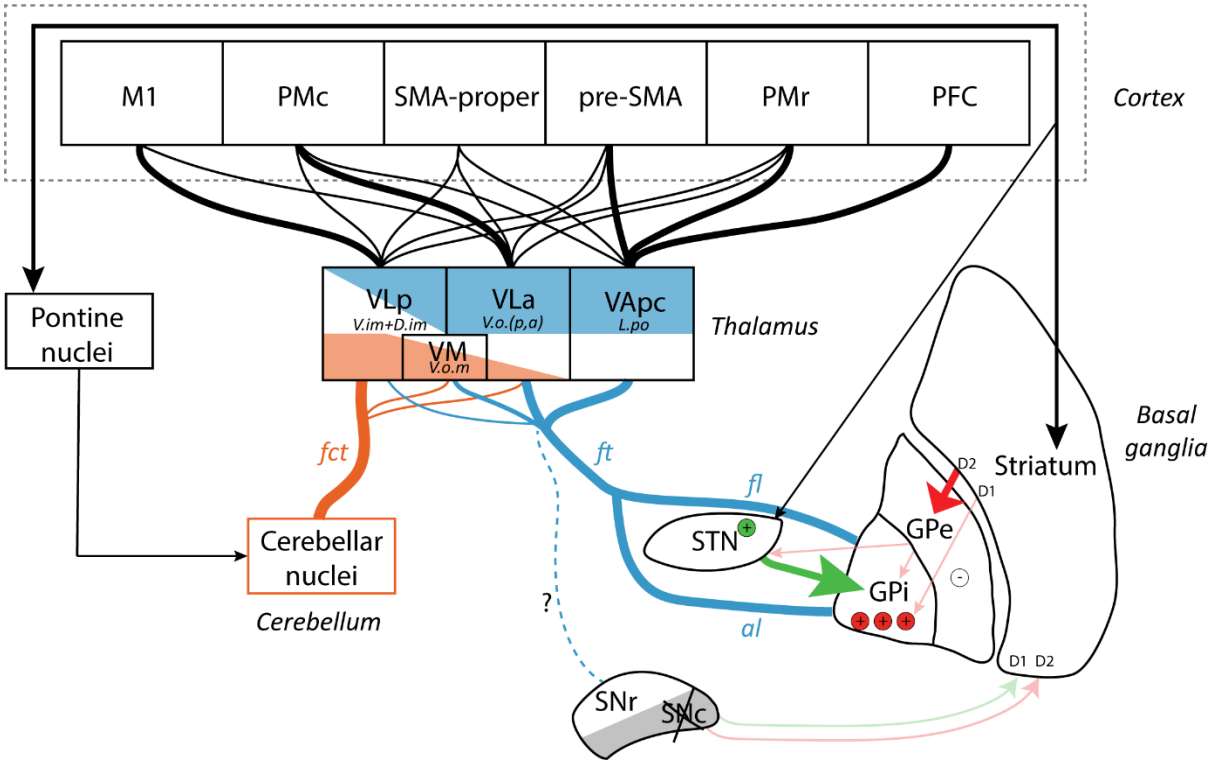


Figure 3: see legend Fig. 2

Summary of ablative approaches in PD (Radiofrequency lesioning, Gamma Knife or MRgFUS)

In a context of permanent increased excitation of the GPi and disinhibition of the STN, the following surgical targets can be proposed. Every target has its strength and limitations. Our work focuses on the pallidothalamic tract for the reasons detailed later in the text.

The major anatomical sites used as surgical targets in advanced and therapy-resistant PD are depicted in the following figure with numbers 1 to 5 (1: posteroventral pallidotomy, 2: nucleus subthalamotomy, 3: pallidothalamic tractotomy, 4: V.o.a. thalamotomy and 5: V.im. thalamotomy).

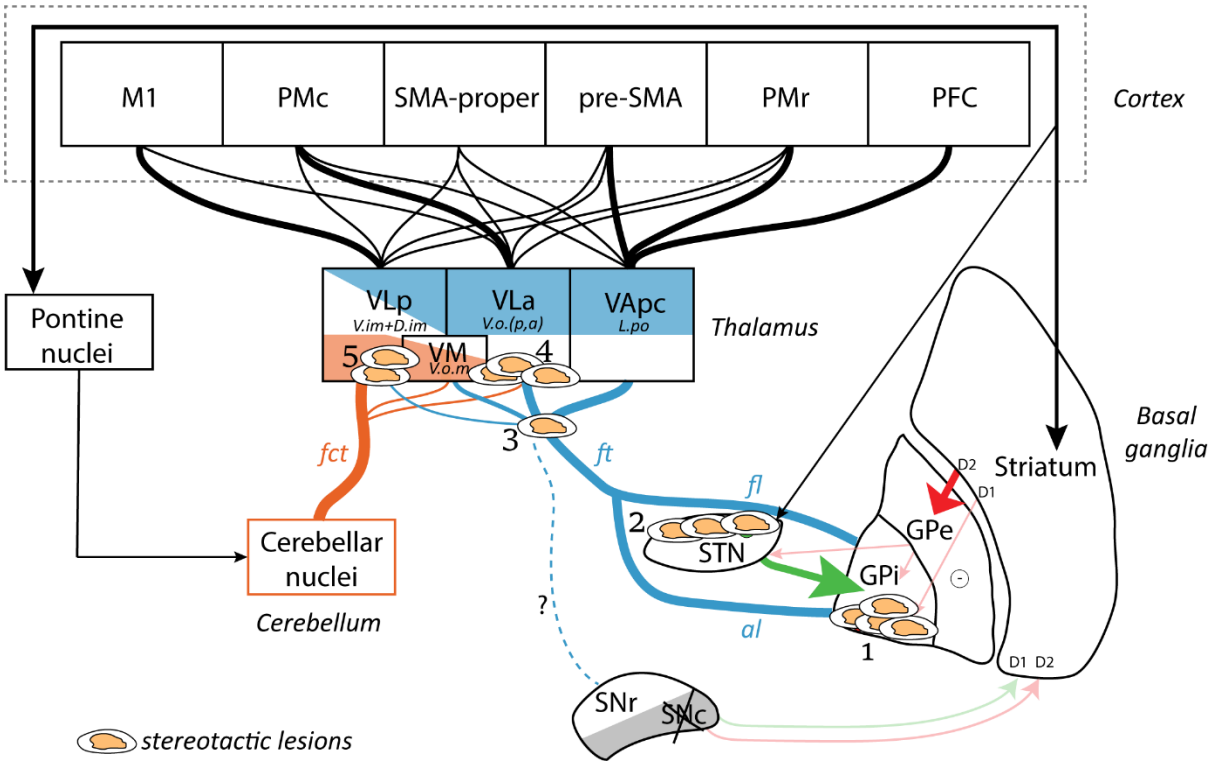


Figure 4: see legend Fig. 2

In the pre-stereotactic era, many surgical operations aimed at treating PD in the central and peripheral nervous system were introduced into clinical practice. Kandel's [21] thorough review of the older functional neurosurgical literature indicates that early operations were often ill-founded, and as a result, many were not effective. Some of these operations, however, provided valuable insights into the pathogenesis of the disease. As mentioned in the "Introduction", Russel Meyers can be considered the "trailblazer" in basal ganglia surgery[18,45]. Meyers reported at a meeting of the Association for Nervous and Mental Disease in New-York in 1940 that in 1939 he had operated on a patient with PD by extirpating the head of the caudate nucleus via an open transventricular approach. The patient did not lose consciousness and showed significant improvement of his Parkinson's symptoms without hemiplegia, thus proving Dandy and Bucy, two authorities in the field, wrong in their assumptions[139]. Meyer's concepts were further developed in the early 1950s by other neurosurgeons who, like him, performed open approaches to the basal ganglia[36,38,154,155].

A well-known example of serendipity from this era is exemplified by Dr. Cooper [156] in 1952. During a mesencephalotomy procedure for a PD patient, he made a "surgical accident" by injuring the anterior choroidal artery and had to ligate the vessel. He then wisely resumed the operation without performing the mesencephalotomy. To his surprise, the patient awakened with no symptoms of Parkinson's disease on the contralateral side to the ligated vessel and no adverse effects. This led Dr. Cooper to advocate for ligation of that vessel as a treatment for parkinsonism, but inconsistent symptom relief was observed due to the variability in the territory supplied by the artery. He later realized that the globus pallidus was commonly supplied by that vessel and advocated alcohol injection or chemopallidectomy as a surgical treatment of PD.

Stereotactic surgery for PD was introduced by Spiegel and Wycis[19] in 1947, with initial targeting the internal segment of the globus pallidus and the ansa lenticularis[157]. Soon, similar operations were proposed by other groups around the world, including Talairach, Riechert and Mundinger, Leksell, Narabayashi and Okuma, Guiot, Cooper, Gillingham, Bertrand, Broager, Aronson and Walker, Obrador, Laitinen and Kandel, among others. By the end of the 1950s, the Freiburg (in Breisgau) school recommended changing the surgical target from the internal segment of the globus pallidus to the ventral lateral thalamus[47,50], and this was adopted by many groups worldwide[21,28,158–168]. Cooper, a prominent neurosurgeon of the era, performed thousands of surgeries in New York[33]. Spiegel and Wycis[13,169] then proposed targeting the subthalamus in the Forel fields[170], a procedure they called "campotomy" (from

the latin campus). This was further developed by Mundinger[12] and other groups[27,171–175]. The Freiburg school, with anatomist Hassler, suggested that the effective lesioning for rigidity and tremor must involve the dorsal field of H1[39], i.e. the pallidothalamic tract just below the dorsal thalamus. Different target combinations were also proposed[21,176]. The proposal of the Centre Médian (CM) as target for PD showed promise, but was not widely adopted[177–180].

50s-early 70s

During the 1950s and until end of the 1960s, and introduction of L-DOPA, stereotactic surgery spread to all continents. According to a survey reported by Spiegel in 1969[181], 11'000 stereotactic interventions were performed at 38 centres between 1965 and 1968. Since introduction of stereotaxy in 1947 and 1965, the same author reports over 37'000 operations recorded worldwide. The number of operations per clinic was much higher compared to present-day high-volume centres, which barely operate over 100 cases per year. Currently, only a few university hospitals in Switzerland reach 20 cases per year. Cooper in New-York performed surgeries on 2362 patients between 1965 and 1968, while Laitinen in Sweden and Riechert in Germany reported over 300 cases per year[181].

Bilateral operations

Parkinson is in most cases a bilateral disease. The early studies of the 1960s demonstrated similar efficacy of operations when operating on the second brain hemisphere. It is interesting to note that despite the lack of any other efficient treatment at that time, surgeons only performed bilateral interventions in a limited number of cases (e.g. 15-25% to a maximum of 35% for Cooper, according to Waltz et al.[182]). The frequency of dysarthria and mental impairments after the second operation, in particular after bilateral thalamotomy along with other surgical risks such as infection, bleeding or electrode shift, and thus neurological deficits, can explain this cautious approach[30,33,37,50,183–185]. Bilateral stereotactic interventions were thus more commonly suggested for younger patients. Cooper[33], for example warned against bilateral interventions for patients over 65 years.

The introduction of L-DOPA in the treatment of Parkinsonism temporarily slowed further developments in the field of stereotactic functional neurosurgery. L-DOPA became a well-established and effective treatment, providing relief to patients and their relatives. However, therapy-resistance, i.e., side-effects, partial symptom control, fluctuations, or dyskinesias appeared over time in a significant number of patients. This led to the re-actualization and refinement of surgical approaches of the past, as exemplified by Laitinen[186] in the late 1980s

and Jeanmonod[14,15,187] in the early 1990s, among others. These procedures were planned and guided with improved imaging capabilities (CT and MR imaging), but still had to be performed using radiofrequency lesioning (RFL).

During the 25 years between the introduction of L-DOPA as a standard antiparkinsonian treatment and the seminal paper of Laitinen in 1992[186] reviving the modified pallidotomy called posteroventral pallidotomy (PVP) of Leksell[188] and the "rebirth" of the field[189], stereotaxic functional neurosurgery surly did not stop but definitely went out of fashion (at least in publications).

In the 90s and early 2000s, the field was enriched by several animal models of the basal ganglia and other systems[190–192], as well as improved by advanced intraoperative electrophysiology[193] and new imaging capabilities. During this period, surgical approaches for treating PD mainly involved uni- and bilateral PVP[186,193–210,210–216]. Thalamotomy and pallidotomy were re-explored using Gamma Knife technology[60,63,70,72,75,76,217–224], while subthalamic approaches had to be rediscovered[14,15]. Nota bene, the radiofrequency PVP is still occasionally performed in 2022 by a few surgeons who received training in lesioning functional neurosurgery[189].

The uncertainty caused by brain shift during radiofrequency (RF) electrode insertion and subsequent neurological deficits produced by misplaced thermolesions have been crucial in the development of deep brain stimulation (DBS) techniques, which have dominated the filed of functional neurosurgery for the past 20 years or more.

The advent of deep brain stimulation[225] and its "reversibility" dramatically changed the field of functional neurosurgery. Spiegel was a trained neurologist who authored many neurosurgical papers from the 1940s onward. He was an exception in a field dominated by neurosurgeons reporting their operations. The technology of DBS suddenly required more time-consuming postoperative patient care, such as re-programming the devices, which was taken care of by neurologists in many centres instead of the operating surgeons.

This evolution is clearly apparent in authorship positions of major clinical papers, with a growing number of neurologists among first or last authors[226–228]. The functional neurosurgical operation became, particularly in case of PD and in Europe, a "multidisciplinary endeavor" with neurologists at its centre discussing and deciding to operate on a patient and the neurosurgeon and the neurophysiologist in a position of mere technicians of it. Some functional neurosurgeons in Europe only see PD patients briefly

before implantation of DBS for the purpose of informed consent but do not examine their patients before and even less after the surgery. From a legal perspective and most in contradiction with the multidisciplinary approach, the surgeon remains the sole responsible of the operation and its consequences.

Presently, the DBS technique dominates the field of stereotactic functional neurosurgery and is present in nearly every major neurosurgical centre over the worldwide.

MRgFUS, a "second rebirth" of ablative stereotactic functional neurosurgery

Due to the limited use of RF ablations in PD only under special circumstances such as DBS failure or financial constraints in non-first world countries and the marginal use of Gamma Knife in treating PD[60,62,63,70,72,219,220,222,229], MRgFUS presents an opportunity for a "second birth" or resurgence of lesioning functional neurosurgery as a viable treatment option for PD.

The study of Magara et al.[5], which was published in 2014 and used the MRgFUS for the first time in PD, opened the field with promising results. In this study, MRgFUS was applied to the pallidothalamic tract unilaterally in thirteen patients. The authors targeted the pallidothalamic fibres on their way to the thalamus, following the path set by Meyers, who attempted to interrupt the pallidofugal fibres in PD along this path in the late 1950s using a focused ultrasound technology device (which required a large craniotomy[87]) with some success according to postmortem specimen.

This first study led to further publications examining the safety and efficacy of MRgFUS pallidothalamic tractotomy (PTT) unilaterally and bilaterally in the years that followed[8–11,146]. The completion of an international multi-centric trial on bilateral MRgFUS PTT is expected in 2023[230].

In 2015, a case report on successful MRgFUS pallidotomy was published[112]. In 2017, 27 patients participated in a randomized clinical trial to investigate the safety and efficacy of MRgFUS thalamotomy for tremor-dominant PD[110]. And in 2018, MRgFUS lesion of the subthalamic nucleus was performed in ten patients with asymmetric PD[111]. The same group published in 2020, enrolling 40 patients, with 13 of them assigned to a sham procedure[113]. The same approach of lesioning the subthalamic nucleus had already been published using RF more than ten years earlier by the same senior author[231–233]. The high rate of side-effects (15% of hemichorea-ballism) may have originally prevented the authors to pursuing this approach further.

In the meantime, the unilateral MRgFUS pallidotomy was evaluated for safety and efficacy in 20 patients[116]. The results of a large pivotal clinical trial (92 participants) applying unilateral MRgFUS pallidotomy for advanced Parkinson's disease are expected in 2023, with study completion scheduled for end 2025[116,234].

In the following paragraphs, we will detail our contribution in improving the treatment of advanced, and therapy-resistant PD using MRgFUS. Our work began in 2008 with the establishment of the anatomical basis for targeting the pallidothalamic tract in stereotactic space[6]. We traced the course of the pallidothalamic fibre tract in the subthalamic region using multiple staining procedures and integrated the information into the Atlas of the Human Thalamus and Basal Ganglia of Dr. Morel[7]. In order to determine the stereotactic three-dimensional coordinates of these tracts, thalamic and basal ganglia blocks were sectioned parallel to stereotactic planes. In two cases, we performed high-resolution MR examinations before sectioning and used the images for correlations. This early work provided evidence for the clear separation of the cerebellothalamic and pallidothalamic tracts in the subthalamic region up to their thalamic entrance, and established a stereotactic mapping and a preliminary evaluation of the interindividual variability of fibre systems in the subthalamic region. The topic of interindividual variability was studied again in a later contribution with additional histological material[8].

The rationale for a subthalamic approach centered on the pallidothalamic tract at the level of the fields of Forel.

Neuroanatomical data[151,235] indicate that a lesion in the H1 and H2 fields of Forel interrupts a larger proportion of the pallidothalamic input, thus representing extensive thalamic disinhibition. Another advantage of such a target position is the possible interruption of the thalamic inhibitory afferents originating in the substantia nigra pars reticulata[15,236].

Pallidothalamic fibres of the ansa lenticularis and fasciculus lenticularis (or H2 field) join 2-3 mm below the intercommissural plane and are funneled into the thalamic fasciculus (or H1 field of Forel) before reaching the thalamus. Interrupting the pallidothalamic tract at the level of H1 corresponds functionally to a pallidotomy, as the majority of pallidal outputs go through it, but with a smaller lesion size[6].

Although relatively small, the pallidothalamic tract must be sufficiently severed to produce desired lasting clinical improvements. The optimal target volume coverage is the subject of the first of the four following contributions[8].

Since re-actualization of this subthalamic approach centered on the pallidothalamic tract[14,15], other groups (Taira and Horisawa in Japan and Godinho in Brazil) have published their own experience using radiofrequency lesioning in PD and in Dystonia [237–240].

The first clinical experience with MRgFUS PTT was published and collected by repeating sonications on the same spot[5]. This led to partial therapeutic effects in the follow-up evaluations of some patients. Later, longer sonication durations without moving the target were tried, but effective lesions were still too small. This approach was not sufficient and required further developments.

The first of the four papers of this section "Anatomical and technical reappraisal of the pallidothalamic tractotomy with the incisionless transcranial MR-guided focused ultrasound[8]", aimed to provide an optimized planning and operative strategy to perform a pallidothalamic tractotomy (PTT) using the technology of MRgFUS[8] (ExAblate neuro 4000 system of Insightec Ltd.). The motivation to develop this targeting protocol, aiming at better spatial coverage of the PTT target, was given by re-analysis of recurrences of symptoms and partial symptom control in previously operated patients with MRgFUS PTT. According to the manufacturer and confirmed by our previous experience, the focal point of the MRgFUS system measures around 1.5x1.5x3.0 mm^3, which is too small to cover adequately most functional neurosurgical targets with one single spot (e.g., posterior ventral lateral thalamus aka Vim Nucleus, Posteroventral Pallidotomy, Subthalamic Nucleus or Central Lateral Thalamic Nucleus). Increasing the duration and the power of sonications increases the risk of unwanted adjacent tissue heating and side-effects without reaching the desired lesion volume (e.g., ~5,5x5,5x3 mm^3 for a proper PTT target).

This model takes into account interindividual anatomical variability and adopts the strategy of applying small thermolesions with the shortest possible sonication durations while controlling thermal dose and using millimetric displacements of the MRgFUS focal point. Histological sections and maps from 6 human brain hemispheres were analyzed, and outlines of the pallidothalamic tract on myelin-stained sections were drawn and superimposed. This resulted in a standardized PTT target, characterized by 5 to 7 pre-planned target lesion sub-units of 1.5 × 1.5 × 3.0 mm^3, which were performed using focal point displacements and the shortest possible sonication durations under thermal dose control.

Since publication, our standardized PTT target has been slightly modified on a few occasions and remains an ongoing project subjected to constant refinements. The latest PTT target

coordinates are illustrated in Fig. 1 of this manuscript. Compared to the published protocol, some coordinates and the order of sonications have been slightly modified.

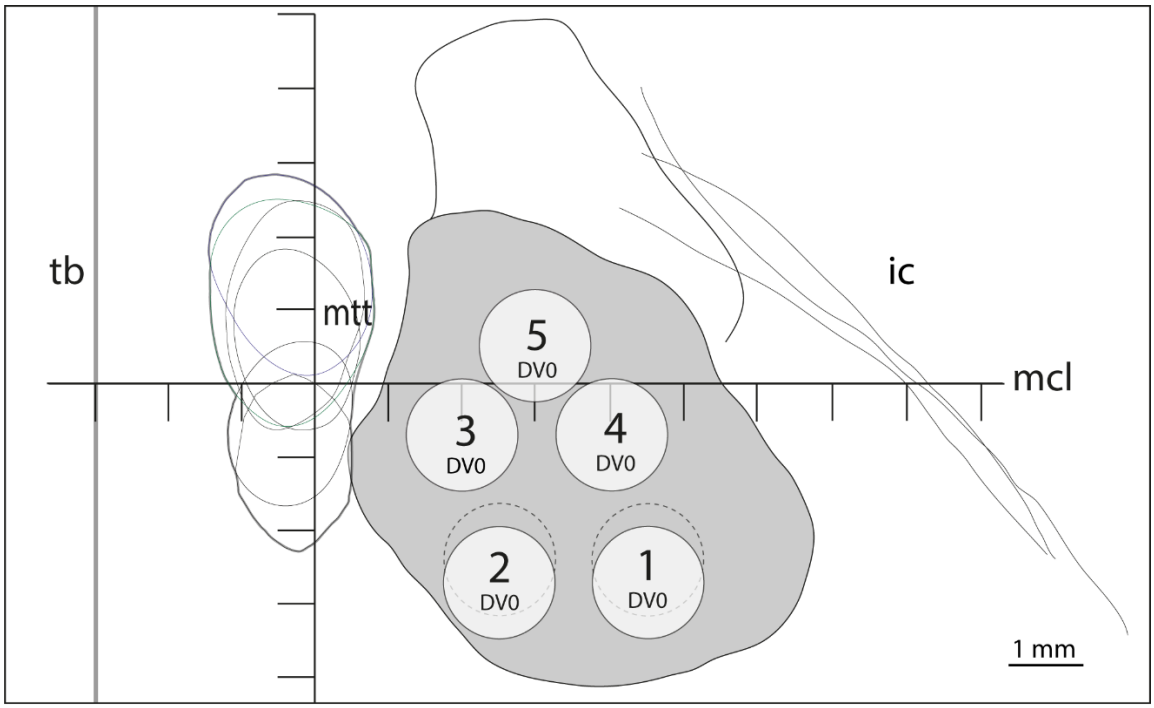


Figure 5: Target lesion sub-units 1 to 5 depicted at the level of the intercommissural plane (DV0). Coordinates of target sub-units; 1: L 7.5 mm from the thalamic border, MCL (mid-intercommissural length)-2.7 mm, DV0 (intercommissural plane); 2: L 5.5, MCL-2.7, DV0; 3: L 5.0, MCL-0.7, DV0; 4: L7.0, MCL-0.7, DV0 or D1 for thalamus height > 16-18 mm and 5: L6.0, MCL+0.5, DV0. mtt (mammillothalamic tract), ic (internal capsule), mcl (mid-commissural line), tb (thalamic border).

Sonications slightly (1 mm) below the intercommissural level are presently performed only seldom. Thermometry monitoring data as well as clinical experience have shown retrospectively that such a protective measure for the mammillothalamic tract is not necessary. The antero-posterior coordinates of target sub-units 1 and 2 were slightly altered in cases where the mid-to-mid intercommissural length is less than 26 mm to MCL-2.2 mm (dotted circles in Fig.1). The antero-posterior and medio-lateral coordinates of target sub-unit 5 were modified to put more distance from the internal capsule. A sixth target sub-unit is sometimes added when the thermal doses are too small to properly cover the pre-planned target volume.

In the second paper “Radiological and thermal dose correlations in pallidothalamic tractotomy with MRgFUS” [9], we investigated the feasibility and predictability of lesion size for the above-mentioned protocol to perform MRgFUS-assisted PTT. MR and thermal dose data were analyzed from 31 MRgFUS interventions in patients with chronic and therapy-

resistant PD using a standardized PTT target with 5 to 7 target lesion sub-units. The proposed approach of using thermal dose steering for multiple target sub-units could be reproduced in 31 interventions with a good lesion size predictability. The mean 240 CEM thermal dose axial diameters were 4.8 and 5.6 mm (SD: 1.0 and 0.9) in the mediolateral and anteroposterior dimensions. Lesion measurements on axial T2 MR images performed a few minutes and 48 hours after the last sonication showed good correlation with the calculated thermal doses. Lesion diameters measured immediately (a few minutes after the last sonication) in the MR were slightly smaller than 18 CEM values, likely reflecting the actual histological lesion size.

At 2 days after the intervention, the axial MR T2 diameters were larger than the calculated 18 CEM values (representing a 50% probability of tissue lesioning) by more than 1 mm (8.9 x 9.1 versus 7.5 x 7.8mm^2). There were no excessively large lesions produced and no encroachment on important adjacent structures such as the internal capsule and mammillothalamic tract with this approach. The study showed the feasibility of repeat interventions using the standardized PTT target (Figure 6) in case of partial symptom control. The decision to use thermal dose monitoring instead of energy- or temperature-based approaches is consistent with the biophysics of focused ultrasound-based tissue thermal lesioning and provides good correlation and prediction. The clinical results, presented in a subsequent contribution, showed a clear reduction of symptom recurrences or partial symptom control, as expected.

The third paper of this section, “MRgFUS pallidothalamic tractotomy for chronic therapy-resistant Parkinson’s disease in 51 consecutive patients: single center experience”[10], aimed to demonstrate the efficacy and risk profile of MRgFUS PTT for treating chronic therapy-resistant PD. This retrospective consecutive case series reflects a clinical routine and was collected between 2017 and 2018. Fifty-two interventions were performed on 47 patients (4 patients were lost to follow-up). All patients benefited from our new target protocol based on anatomical/histological reappraisal and optimization of lesioning strategy using thermal dose control[8]. Fifteen patients received bilateral PTT, and the median follow-up was 12 months. The mean age at the time of the operation was 67 years, and the mean symptom duration was 10 years. This series includes 18% tremor-dominant, 72% mixed and 10% akineto-rigid PD patients according to Rajput et al[241].

Bilateral PTT was performed in 15 patients. Postoperative results revealed percentage reductions of 84% for tremor, 70% for rigidity and 73% for distal hypobradykinesia, all given for the operated side (postoperative off-medicated state compared to baseline on-medication score). Axial items (voice, trunk, and gait) were not significantly improved. Dyskinesias were suppressed contralaterally to the PTT in all patients, as well as pain and dystonia. REM sleep disorders were also absent at follow-up. Patients reported an 88% mean tremor relief, 82% mean global symptom relief on the operated side, and 69% mean global symptom improvement for the whole body. There was no significant change in the Montreal Cognitive Assessment performed at baseline, 2 days and 1 year after PTT. The small group of bilateral PTTs at 1 year follow-up (n=4) did not allow firm conclusions to be drawn at this point. Mean L-DOPA intake was reduced by 55% at 1 year. The results are presented in Tables 2-5 and illustrated in figures 2-6[10].

MRgFUS PTT was shown to be a safe and effective intervention for PD patients, addressing all symptoms with varying degree of effectiveness. We discussed the need to integrate the preoperative state of the thalamocortical network (brain atrophy and cognitive impairments) and the psycho-emotional dimension.

The fourth and final paper of this section "Bilateral MRgFUS pallidothalamic tractotomy for Parkinson's disease with one year follow-up"[11] was the first case series ever published after bilateral MRgFUS treatments in advanced Parkinson's disease.

PD is a bilateral disease in most advanced and therapy-resistant cases. Despite all efforts of the neurological and neurosurgical community, a large number of patients are reluctant to undergo DBS surgery, even when they meet the criteria for referral to a DBS center[242]. In light of improved lesioning accuracy, reduced bleeding risk, and suppression of infectious risks, and despite the long-standing concerns about bilateral approaches, there was a need to investigate bilateral MRgFUS interventions for PD. The choice of target has been detailed in previous paragraphs. So called "asymmetric" lesioning has been tried in the past by some groups (thalamotomy on one side, pallidotomy on the other) but results did not show superiority[184] and were abandoned in most centers.

Early bilateral series were mostly published during the 1960s[21,27,30,33,37,43,47,50,167–169,174,175,180,184,188], in the pre-L-DOPA era, when postencephalitic patients were still numerous in need of neurosurgical help. Considering the limited imaging guidance and lack of modern refined electrophysiological monitoring, reported results on motor functions (although

lacking modern criteria for reporting) were impressive. Patients operated on were younger and were not tested for therapy-resistance (for the obvious reason that L-DOPA was not available).

Case series of bilateral pallidotomies followed the work of Laitinen[186] on the posteroventral pallidotomy with the radiofrequency technique mainly during the 1990s[195–206,243,244] until the DBS technique came to dominate the field of functional neurosurgery.

In this final contribution, we present the results of a series of 10 patients who were followed for 1 year after receiving bilateral PTT, either staged or contemporaneous (the mean time frame between baseline UPDRS score and 1 year after the second side was 36 months). The mean total UPDRS score off-medication at 1 year after the second PTT was reduced by 52% compared to the baseline on-medication score. In line with previous results from unilateral PTTs, the total tremor (both sides of the body) was reduced by 91%, total distal rigidity by 67% and distal hypobradykinesia by 54%. The mean scores for axial items (taken from the UPDRS scale), the postural instability and the gait, were only slightly improved but not statistically significant. Speech difficulties, including hypophonia, tachyphemia, and speech initiation, increase by 58% ($p=0.06$). Dyskinesias were suppressed in 4 out of 4 patients, dystonia in 4 out of 5, and sleep disorders in 3 out of 4. There was a 89% reduction in mean subjective pain, and mean L-DOPA intake was reduced from 690 mg down to 110 mg per day. The results suggest a strong efficiency of bilateral PTT in controlling tremor, distal rigidity, distal hypobradykinesia, dyskinesias, dystonia, and pain compared to the best medical treatment at baseline over a mean period of 36 months.

As gait, postural stability, and other axial functions did not show significant improvement, surgery, as it has been well recognized years ago, should be offered cautiously to patients primarily suffering from symptoms affecting these dimensions. It is important to discuss the issue of speech and the potential need for speech therapy with patients and their relatives before undergoing bilateral PTT. This is because there is no evidence for capsular involvement or any other surgical complication responsible for (and thus avoidable) speech-related effects. It is also important to note that chronic stimulation of the subthalamic nucleus has also been shown to result in speech deterioration in up to 69% of patients. We discuss the issue of speech and the other axial functions relevant in PD (gait and postural stability) as well as the importance of psycho-emotional factors. Additionally, we emphasize the critical

role of psycho-emotional factors in speech and other axial functions relevant in Parkinson's disease, such as gait and postural stability.

Since the publication of these four articles describing the targeting anatomy, strategy, the radiological and thermal dose correlations, and first clinical results on uni- and later bilateral treatments, Horisawa et al.[237] have been able to replicate this approach in a prospective series of akineto-rigid Parkinson's patients, a particularly difficult patient group according to many prominent functional neurosurgeons[21,33,184]. A multi-centric international trial is presently investigating bilateral PTT surgery with the MRgFUS in 50 patients, which demonstrates the global interest in this approach[230](NCT04728295).

Global comparison between MRgFUS and DBS techniques (addendum June 2024)

Currently, the DBS technique is the standard of care in most industrialized countries for treating advanced PD. This preference is supported up by multicenter trials and long-term follow-ups, with studies supporting its use dating back to the early 90s. According to Sarica's analysis published in 2023, the most frequent indications for DBS between 1993 and 2017 in the USA were PD (67%), ET (24%) and dystonia (4%)[245].

In contrast, the first study on MRgFUS in functional neurosurgery was published in 2009 for neuropathic pain. The initial MRgFUS series in movement disorders were published in 2013[246] (ET) and 2014[5] (PD), over twenty years after the first DBS trials.

A direct comparison between MRgFUS and DBS techniques is still not possible for any functional neurosurgical indication, as no randomized reference studies have compared the two. However, the ability to conduct randomized, sham-controlled clinical trials with MRgFUS has enabled it to become a standard of care for the treatment of ET within just ten years. This is due to its clinical efficacy being equivalent to DBS but with reduced risks and lower costs. Since 2022, German guidelines have recommended MRgFUS as a first-line treatment in therapy-refractory ET[247]. The FDA validated bilateral MRgFUS thalamotomy for ET[102,103,248] at the end of 2022.

The situation for advanced PD is more complex due to the multiplicity of symptoms and the heterogeneity of PD patients, making it difficult to standardize the surgical approach. As aforementioned, this has been a recurrent topic of discussion over the past eighty years and is unlikely to be resolved soon. Even with the relatively standardized DBS approach, the neurosurgical target can be either the STN, GPi or VLpv (Vim). Most MRgFUS studies in PD have selected patients based on tremor-dominant forms and asymmetric symptoms, which was generally not the case in DBS studies.

At this stage, the published efficacy, in terms of symptom control, seems to favor PTT- and STN-MRgFUS over DBS[10,111,113]. However, the small size of the cohorts, short follow-up durations and the fact that the studies were monocentric and unilateral[5,10,97,110,113,114,231,249] make direct comparisons impractical. A recent multicentric randomized and sham-controlled trial of unilateral MRgFUS pallidotomy yielded positive results, but the low magnitude of clinical improvements makes it difficult to justify given the side-effect profile[250]. As previously

suggested, the pallidum seems to lie at the limit of the current treatment envelope within the brain for MRgFUS, making MRgFUS pallidotomy likely to remain a secondary target. Furthermore, advanced PD is mostly a bilateral disease and ideally should be treated on both hemispheres. This is a significant advantage of the DBS technique, which allows bilateral deep brain electrode implantation in one session. To determine how lesioning with MRgFUS[251], regardless of the chosen target, fares compared to DBS in terms of efficacy and side-effect profile, more bilateral studies[11,252] with a large number of patients and longer follow-up are of needed[253].

The role of MRgFUS in the treatment of advanced PD disease is yet to be fully defined. It remains to be seen which target(s) yield the best results for specific patient subgroups, and how these positive clinical results will stand the test of time. The reproducibility of results must be demonstrated by more neurosurgical groups applying the protocols, ideally in large randomized multicenter series. In conclusion, there is still much work to be done to establish the MRgFUS technique in advanced PD.

	DBS in PD	MRgFUS in PD
Pros	Standardized treatments	Higher patient acceptance
	Many trained neurosurgeons	Very low risk of bleeding (0 over 650 in Solothurn)
	Intraoperative neurophysiology	No risk of infection
	Possibility of stopping operations or later removing equipment	Higher targeting accuracy
	No risk of placing a permanent lesion off-target	Real time monitoring (MR-guided)
	Possibility to treat both hemispheres in one session	No implanted material
	Numerous publications and some long-term follow-up	No troubleshooting because of material failure, no device maintenance
	Good acceptance by neurologists	Preliminary data on efficacy and drug reduction are encouraging
	Strong support from industry	Randomized sham-controlled trials possible (done for ET and PD)
	Better reimbursements for the clinic	Ambulatory or short hospital stay
Cons	Low patient acceptance	No standardized targets
	Bleeding risk (2-4 %)	Few experienced neurosurgeons
	Risk of infection	No intraoperative neurophysiology
	Lower accuracy due to brain shift	Lesioning technique and thus definitive
	Loss of effect over time (“habituation”)	Fewer studies with long term data
	Costs of implantation	Higher dependance on neurosurgeon’s experience
	Maintenance and troubleshooting costs	Staged bilateral interventions recommended
	Implant not always compatible with high-field MR (3-7 Tesla). Need to check neurostimulator after MR	High degree of skepticism among neurologists
	Little reduction in medication	Start-up company
	Operating room	Business case very challenging
	Sham-controlled trials difficult due to implanted material	MR time slots
	Intensive care unit	

Section three: Incisionless MR-guided focused ultrasound neurosurgery for chronic therapy-resistant essential tremor

Gallay MN, Moser D, Rossi F, Pourtehrani P, Magara AE, Kowalski M, et al: Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. Journal of Therapeutic Ultrasound 4:5, **2016**

Gallay MN, Moser D, Jeanmonod D: MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. J Neurosurg Feb 7:1-10, **2020**

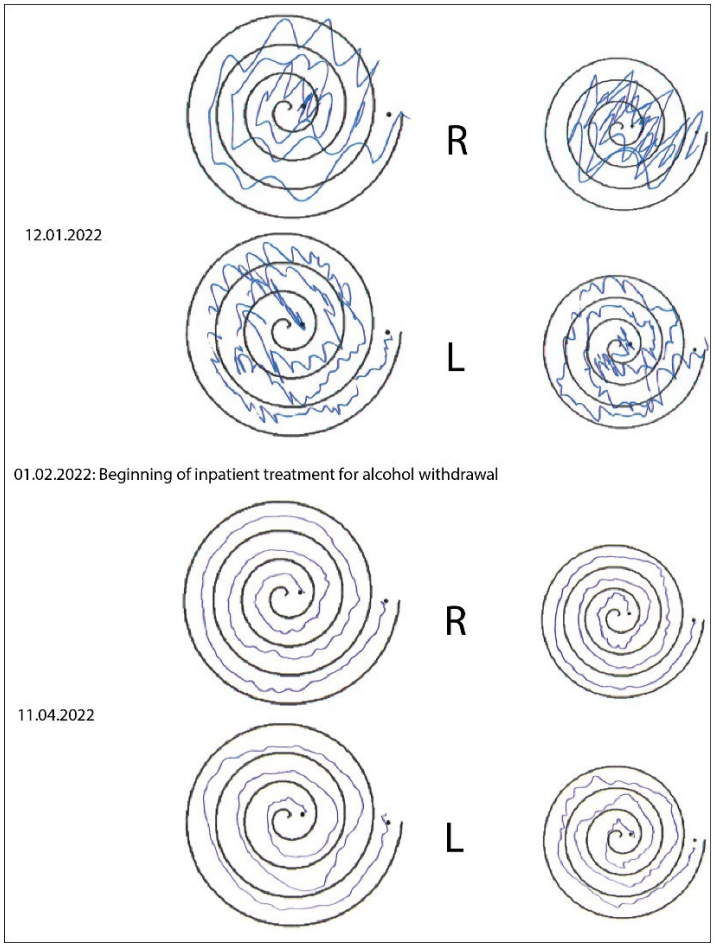
Essential tremor (ET), also known as benign ET or familial tremor, is the most common type of pathological tremor in humans, with a prevalence rate ranging from 0.4% to 6 %. It affects approximately 1% of the population and 4-5% of people aged over 65 years[254] but remains frequently undiagnosed. The condition is more common in men, progresses slowly, and often has a hereditary pattern. The diagnosis of ET is made through a clinical examination and does not qualify as a specific disease[255]. It is a syndrome characterized by an action tremor (kinetic and/or postural) that predominantly affects both upper extremities. The tremor usually starts simultaneously in both upper extremities, but can also occur in the head, face/jaw, voice, tongue, trunk and lower limbs. According to Elble [255], the term "essential tremor" was first used by Burresi and his student Rubini in 1874 to describe patients with action tremor and no other neurological signs, and early writers noted that this condition was often hereditary" [256,257].

Approximately 50% of ET patients have a family history of tremor. The age of onset of ET may be lower in cases with of positive family history[258]. ET is characterized by a rhythmic oscillation of agonist and antagonist muscles, typically at a frequency between 8 Hz and 12 Hz. According to our personal observations on ET patients who were candidates for MRgFUS, the average frequency of tremor when reaching high intensities seems to be much lower, at around 5-6 Hz. The amplitude of the kinetic tremor is more severe than the postural tremor in around 95% of cases[259]. Rest tremor can occur in patients with longstanding disease[254]. According to Louis et al. 2015[260], its prevalence ranges between 1.9% in a population-based setting and 46.4% in the brain bank study[261]. In one study, kinetic leg

tremor was found in 44% (28 out of 63 patients) of ET patients, compared to 14.3% of controls (9 out of 43)[262]. In other series kinetic tremor or the lower limbs was found in 27%[263] or 28.6%[264] of ET patients, respectively.

Head tremors are typically more common in women and tend to increase with age, but not disease duration. As many as 30-60% of patients may develop head (neck) tremors[265]. Nearly half of patients (48.7%) with head tremors are unaware of its presence, according to a study by Eken et al.[266]. Alcohol consumption has been shown to reduce tremors in 74% of patients[267]. Objective testing found tremor reduction after alcohol consumption (targeted blood alcohol concentration of 0.6 $^{0}/_{00}$) in 46% of patients[268]. However, alcohol often causes a rebound effect with increased tremors the next morning. The dramatic suppression of ET by alcohol is not a reliable diagnostic tool[269–271].

Contrary to the traditional belief that alcohol only reduces tremors in ET patients, the following figure illustrates the spontaneous reduction of a severe and invalidating bilateral tremor in a patient who was consuming approximately two bottles of wine daily, two months after completely abstaining from alcohol.



ET is often accompanied by coordination deficits. Patients with ET perform worse than age-matched controls in balance testing[272–275].

Interestingly, audiology testing has shown high-frequency sensorineural hearing loss in ET patients[276]. Hearing impairment was found in 39% of ET patients (96 out of 248) compared to 29.4% (1371 out of 4669) of controls[277]. The coexistence of PD was found in 6.1%, dystonia in 6.9% and 1.8% had a myoclonus in addition to ET.

The 2018 consensus statement of the Movement Disorder Society on tremor introduced a new term: Essential Tremor-plus (ET-plus). However, we have not adopted this new diagnosis due to lack of solid evidence. According to Dr. Louis ED[278], an authority in the field of movement disorders, "this term is uncertainly defined as tremor with the characteristics of ET, with additional neurological signs of uncertain clinical significance. If ET-plus had been defined based on a difference in underlying pathology or an appreciable difference in prognosis, it would have a valid scientific rationale, as does the term Parkinson-plus. However, there is no such evidence, so the basis for the term is questionable (…) We caution against coining new terms that are not supported by a firm scientific basis and encourage research into the creation of essential tremor subsets that are defined with respect to differences in underlying causes or pathophysiology."

The pathophysiology of ET remained elusive until the beginning of the 21st century. Animal models of tremor, such as the harmaline models, have provided important insights into the mechanisms of tremor, but no specific transgenic animal models of ET currently exist[279–282]. Changes in the cerebellum, and more precisely in the Purkinje cells (PC) population, are a common finding across most recent studies[283–286], despite some contradicting findings by other groups[287,288]. Purkinje cell losses and changes in their different cell compartments (dendrites, body, axon, basket cell processes, and climbing fibre-Purkinje connections) have been described, supporting the possibility of reduced inhibition of the dentate nucleus and thus overactivation of the VLp through the cerebellothalamic tract.

ET is often refractory to conservative treatments and has the potential to cause severe disability. According to Shankar[254], existing drugs for ET are suboptimal. Many patients do not respond to them, and those who do may not have a significant improvement in their daily life. In a series of 528 ET patients, one-half or more of the treated patients had stopped the medication prescribed (for the four most used medications: propranolol, primidone, diazepam and topiramate). Neurologists often propose drug polytherapy when monotherapy provides a

partial response, but it is, in most cases, insufficient and side-effects of those drugs are often non-negligible. Common side-effects of Propranolol (a selective β adrenergic receptor antagonist) are bradycardia, bronchospasm, hypotension, fatigue, lightheadedness, sexual dysfunction, and depression. Primidone (a barbiturate) can cause dizziness, malaise, and very often fatigue. Topiramate (an anti-epileptic) may produce paresthesia, impaired attention, decreased appetite, nausea, fatigue, and memory difficulties. Of all possible drugs prescribed against ET, only propranolol, primidone and topiramate are first line therapies.

In his review from 2013, Elble[255] concluded, "ET is a deceivingly simple clinical syndrome that is associated with a complex web of clinical, pathological, and genetic phenomena. The heterogeneity of ET is probably a major reason for our poor success in finding effective drugs and disease-causing genes. However, the highly effective and nonspecific tremorolytic effect of stereotactic thalamic/subthalamic surgery should serve as a continuing reminder that a complete understanding of a heterogeneous disorder is not always necessary for finding an effective treatment."

Stereotactic interventions against ET

To justify a functional neurosurgical intervention in the brain, patients must meet strict and clear clinical criteria, despite advances in technology and reduction of morbidity. In the case of ET, the intensity of the tremor must reach a 3 out of 4. In special circumstances, a rating of 2-3/4 in a young, professionally active patient may be acceptable. Resistance to pharmacological treatment or the occurrence of drug-related side effects that prevent their use must be established, and the patient's quality of life must be significantly diminished.

Surgical treatment of ET through stereotactic operations started around10 to15 years later than for PD. The delay is speculated to be due to the mean age of the patients, as PD patients were likely much younger, and because ET was considered to be relatively benign compared to PD. Nevertheless, the first series of cases were published from the early 1960s onward [13,29,34,35,47,172,289–295].

Already in the late 1960s and early 1970s, stereotactic surgery against ET aimed neuroanatomical structures located on the cerebello(dentato)-thalamic axis, some targeting directly the ventral part of the posterior ventral lateral nucleus of the thalamus (VLp), also called ventral intermediate nucleus according to Hassler (Vim)[32,34,35,294,296–300]. Other groups explored the posterior subthalamic area (PSA) also named prelemniscal radiation or posterior zona incerta, and thus targeted the efferent fibres from the cerebellar nuclei (the dentate

nucleus mostly) on their way to the motor thalamus[13,29,47,172,289,290]. Published results of these approaches and particularly the one in the posterior subthalamus, considering the technical limitations of their time, were highly promising. Since the end of the 90s and development of the DBS techniques, RF lesioning against ET has been virtually inexistant or at least not reported. Comparison of surgical techniques against ET (DBS, radiofrequency (RF) lesioning, Gamma Knife and MRgFUS) can be found at page 8 of our first contribution[16].

MRgFUS against ET

Elias and collaborators were the first to publish in 2013 a pilot study performing MRgFUS thalamotomy against chronic and therapy-resistant ET in more than 10 patients and followed 1 year after the intervention[246]. The same leading author coordinated a randomized sham-controlled multicentric trial in 2016 demonstrating the safety and relative efficacy of MRgFUS in ET[93]. These first studies, followed by others[91,95–99,101,102,114,120,301–303], were not able to replicate the rates of tremor control obtained by RF lesioning, deep brain stimulation[304] and Gamma Knife surgery[76,223]. According to Abe et al.[101] for the Japanese Multicenter Single-Arm Study on MRgFUS thalamotomy, "Unilateral MRgFUS thalamotomy is effective in sustained alleviation of tremor symptoms, which results in significant improvements in the quality of life with minimal and transitory adverse effects". Main side-effects of the MRgFUS thalamotomy (pars ventralis of the VLp, or Vim) according to the study of Elias 2016[93] were paresthesia or numbness (38% total, 14% still present at 1 year), taste disturbances (5%, 4% at 1 year), gait disturbances (36%, 9% at 1 year), dysmetria (12%, 4% at 1 year), and limb weakness (4%, 2% at 1 year). There was no bleeding or infection.

Only recently, Lak et al. published a retrospective series of MRgFUS Vim thalamotomies performed by a single experienced group (160 consecutive cases) showing a tremor control over 80% tremor at 1 year follow-up[305].

Our first contribution "Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy" [16], was the first case series that applied MRgFUS to perform a uni- or bilateral cerebellothalamic tractotomy (MRgFUS CTT) in ET, and the second largest series on MRgFUS in ET after Elias and collaborators[246] (since the introduction of the MRgFUS into the field of stereotactic functional neurosurgery[93]). Twenty-one consecutive patients suffering from chronic and therapy-resistant ET, who were treated in

our center with at least 3 months follow-up, were included. Three patients received bilateral treatment with 1-year interval. The evolution of seven patients with a Hand Function Score (HF32) over 28 points (most severe ET cases) was analyzed separately and differentiated itself from the others. The reduction of the Hand Function score 16 (HF16), which comprises 4 items testing the tremor in the operated upper extremity, was 92% in the first group and 41% in the second group at 3 months, and remained stable at 1 year (90% and 40% respectively). The mean patient estimation of global tremor relief after CTT was 92% at 2 days and 77% at 1 year follow-up. No bleeding or infections occurred, but a worsening of pre-existing gait instability was found in five patients. Only one patient did not fully recover their original walking ability, with a score for tandem gait 0.5 points worse than preoperatively. There were no other side effects.

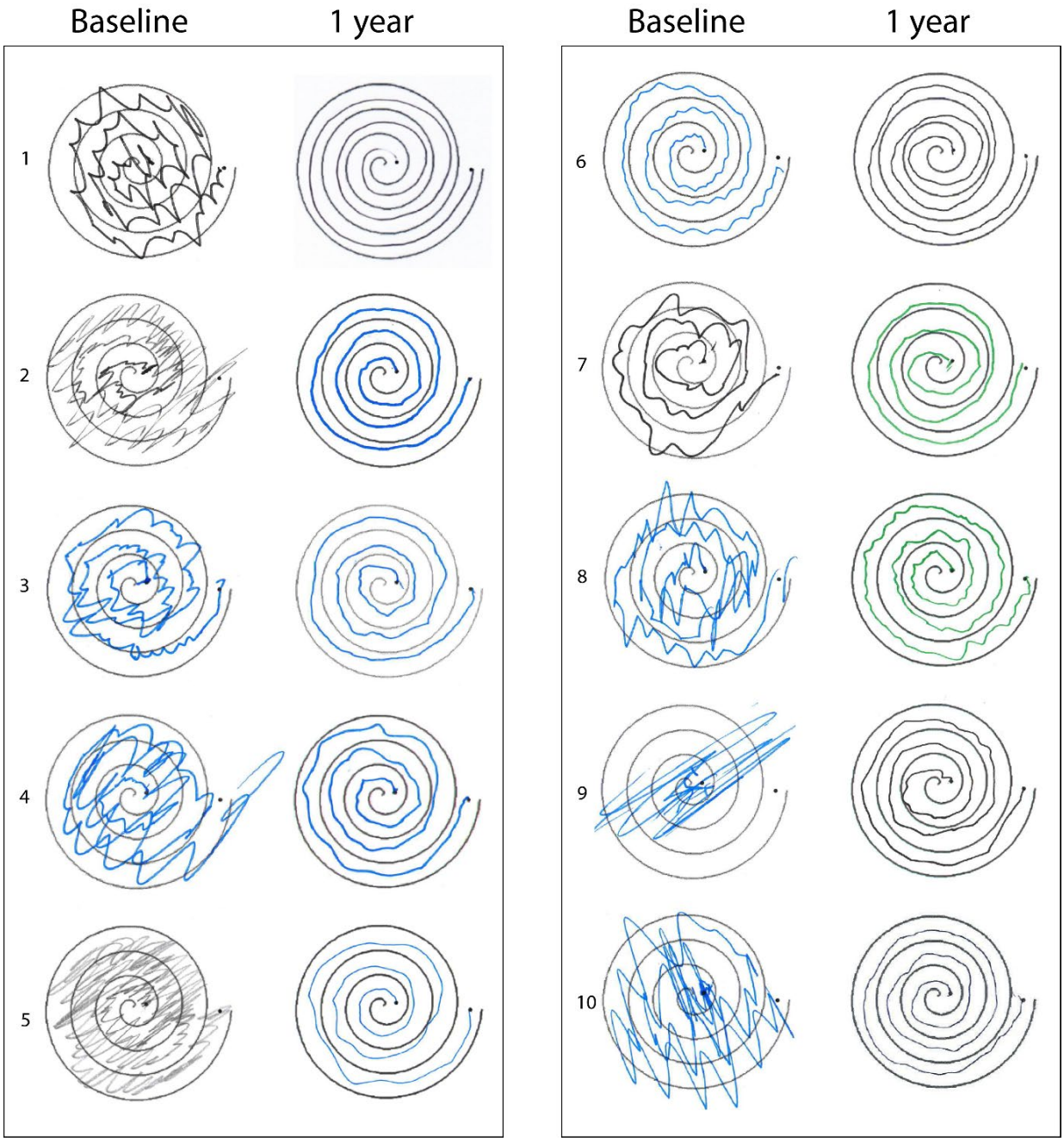
This approach was later replicated by another group with similar efficacy and side-effect profile[108]. During the time frame between our two contributions (2016-2020), clinical results obtained with the MRgFUS technique by others on unilateral tremor control have shown some degree of variability or limitations[93,98,300,301,306]. In our first case series published on the MRgFUS CTT, the mean unilateral and bilateral tremor reductions stood at more than 70 % for the treated side, but significant differences were seen between patients[16].

The motivation behind our second contribution, “MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results” was to enhance target coverage and thus improve efficacy, such as tremor control and its consistency. We conducted a histological reappraisal of the CTT target and proposed a new targeting strategy, which was based on 1) MR visualization of the center of the red nucleus (mRN) and 2) application of preplanned target subunits realized with short sonications under thermal dose control[17].

A detailed analysis of the localization of the histological anatomy of the cerebellothalamic tract in the posterior subthalamic area was performed on the original histological sections and maps of four human brain hemispheres, which were only partially published in different versions of Dr. Morel’s Stereotactic Atlas of the Human Thalamus and Basal Ganglia. A reappraisal of the interindividual variations of the cerebellothalamic tract, normalized to the centre of the red nucleus (mRN) in the axial stereotactic plane, was conducted to provide maximal coverage of the tract without affecting surrounding neuroanatomical structures. This histological reappraisal led the authors to propose a standardized targeting protocol for

MRgFUS CTT. This approach is similar to that already proposed for targeting the pallidothalamic tract in PD, which includes a maximal coverage of the tract with 2 to 3 target lesion subunits. The target lesion subunits were deployed on the tract with the goal of optimizing target coverage and minimizing risks for adjacent structures such as the mammillothalamic tract, subthalamic nucleus, and somatosensory thalamus.

Ten consecutive ET patients were followed over a 1-year period after undergoing MRgFUS CTT according to the proposed protocol. The primary endpoints were subjective tremor relief, Clinical Rating Scale for Tremor (CRST) score, activities of daily living (ADL) score, and the hand function (HF) scores HF16 and HF32. Thermal doses were calculated for 18 and 240 cumulative equivalent minutes at 43°C and were correlated with intraoperative and 2-days postoperative T2-weighted MR images. The mean baseline CRST score was 48 ± 12 which decreased to 16 ± 7 at 3 months, and remained at 17 ± 8 at 1 year. On average, the patients rated their tremor relief on the operated side as 95% after 2 days, 96% at 3 months, and 93% at 1 year. The mean HF16 was 11.0 ± 2.1 at baseline, which decreased to 0.7 ± 0.7 at 3 months and 0.8 ± 0.9 at 1 year (a 93% reduction on average). There was a 51% reduction in the mean ADL score at 1 year. Three patients experienced increased gait difficulties, detectable only during tandem gait, while two patients experienced improvement at 1 year. There were no instances of dysarthria, bleeding, or infection reported.



Source: Fig.7 in **Gallay MN**, Moser D, Jeanmonod D: MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. J Neurosurg Feb 7:1-10, **2020**

Radiological outcome

Pearson's analysis showed excellent correlations between 18-CEM and 240-CEM thermal doses (r = 0.79), between 18-CEM thermal dose surfaces and intraoperative axial MR T2 lesion surfaces (r = 0.77), and between axial MR T2 surfaces 2 days after the procedure and 18- CEM thermal doses (r = 0.8), 240-CEM thermal doses (r = 0.76), and intraoperative axial T2 surfaces (r = 0.83). The measured MR T2 volumes of lesions at 2 days showed good correlations with the extrapolated 18-CEM (r = 0.69) and 240-CEM (r = 0.64) thermal dose volumes.

The results of these adaptations allowed us to achieve consistently high tremor relief (>90%) in a consecutive series of 10 patients.

This series was continued over the next years with over 60 treatments with follow-ups of 1 year or longer. The mean tremor control rated by the patients was 87% (median: 92.5%) at the 1-year follow-up (publication in preparation).

Section four: The Insula of Reil

Gallay DS[×], **Gallay MN**[×], Jeanmonod D, Rouiller EM, Morel A: The insula of Reil revisited: multiarchitectonic organization in macaque monkeys. Cereb Cortex 22:175–190, 2012 ([×]equally contributing authors)

Morel A, **Gallay MN**, Baechler A, Wyss M, Gallay DS: The human insula: Architectonic organization and postmortem MRI registration. Neuroscience 236:117–135, 2013

The insula of Reil, sometimes referred to as the "fifth lobe" of the brain, is buried in the depth of the Sylvian fissure and is therefore not easily accessible. Awareness of the insula's existence dates back to at least 1543, when it was described by Vesalius in his work "De Humani Corporis Fabrica Libri Septem". The term "insula" was introduced by Prussian anatomist Johann Christian Reil in 1809, who focused on this region is his treatise[307].

In contrast to other mesocortical (paralimbic) regions[308] (in particular the cingulate and orbitofrontal cortices), the anatomy of the insula has not, or only minimally, been re-explored since the seminal studies in the 1960s and 1980s[309–312]. These earlier studies still serve as a basis for relating functional and connectivity studies in monkeys. The insula is part of a large mesocortical domain with transitory architectonic characteristics between allo- and isocortex. It is known to have a tripartite division into agranular (or periallocortical), dysgranular (or proisocortical), and granular (or isocortical) sectors[309]. From an evolutionary perspective, it belongs to the four large cortical regions that seem to have greatly expanded in the human brain, along the prefrontal, posterior parietal, and temporal cortex. As neuroanatomist John H. Kaas has noted, "the human insula is amazing in absolute size. Even in proportion to the rest of the brain, the insula in humans is larger than those in apes and other primates"[313]. This assertion is somehow mitigated by Semendeferi et al[314]. After conducting studies using magnetic resonance imaging on brains from apes and humans, the authors found that the human insula appeared to be slightly larger than expected for an ape brain of human size, but the differences were not statistically significant.

The Insula of Reil has received a great deal of attention in recent years due to functional neuroimaging studies, which have provided further evidence of its involvement in a wide range of functions (multimodal), including taste, pain, temperature, touch and internal state[309,315–327]. In the supposedly enlarged human insula, new regions have been identified

that are thought to mediate empathy and social awareness[328,329]. Despite the attention it has received, most of our knowledge about the human insula still comes from neurophysiological and neuroanatomical studies in monkeys[309,315,324,330,331].

Localization in the insula is often related to a bipartite anteroposterior division separated by the central insular sulcus, with different functions attributed to the posterior versus anterior insula. For example, processing of pain has been particularly emphasized in the posterior insula and adjoining opercular areas [326,332–334], while the anterior insula is more implicated in the integration of complex autonomic, cognitive and emotional processes thought to be important in interoceptive awareness [328,335,336]. The possibility to explore in vivo human brain connectivity using probabilistic diffusion tractography and resting-state functional connectivity has provided interesting insights into insular parcellation, although current resolution still prevents close correlations [337–339]. In contrast to numerous neuroimaging studies, relatively little progress has been made in the detailed analysis of the architectonic organization of the human insula in relation to its major gyri and sulci.

The cytoarchitectonic organization of the human brain has been proposed to be similar to that of monkeys, with three major domains (agranular, dysgranular and granular) arranged concentrically around the piriform olfactory cortex at the limen insulae [340]. However, the sparse description and pictorial representation of these domains cannot easily be related to the complex anatomy of the human insula as seen in postmortem and in vivo neuroimaging studies. More recently, two studies have provided deeper insight into cytoarchitectonic organization of the human insula. The first study produced a map to evaluate pathological changes in Alzheimer's disease [341] and showed corresponding overall gradients described by Mesulam and Mufson (1985) and by a tentative representation in a Golgi study of the insula [342]. Using an "observer-independent" approach, Kurth et al.[343] presented a probabilistic map of the posterior insula, which differs somewhat from the other schemes, particularly with regard to the extension of the granular domain.

Other studies focused on the orbital and medial prefrontal cortex[344], including the most anterior part of the insula, have defined several subdivisions based on cyto- and chemoarchitectonic criteria. The same region, also referred to as the fronto-insular cortex, is notable in human and great apes for the presence of large spindle-shaped, bipolar neurons (known as Von Economo neurons or VENs) in layer V. These VENs are similar to those found in the anterior cingulate cortex [335,345–347] and are believed to play a role in intuition and

to be specifically impacted in several neuropsychiatric disorders that result in emotional function deficits[335,347–350].

Establishing correlations between human insular strokes and neurological deficits is challenging due to the rarity of isolated insular stokes and the heterogeneity of clinical presentations, which are predicted by the anatomy of the insula. Insular strokes often result from damage to larger cortical and subcortical areas supplied by the middle cerebral artery, and many deficits may be caused by poor perfusion of surrounding areas such as the opercula, the basal ganglia, or internal capsule.

Open (through craniotomy) or minimal invasive (implantation of depth electrodes in the insular cortex) neurosurgical procedures, in the context of presurgical evaluation of therapy-resistant epilepsy, offer unique opportunities to understand the various functions of the insula[351]. Guillaume & Mazar[352,353] at the end of the 1940s, followed by Penfield & Jasper[354], pioneered the concept of insular cortex epilepsy. The latter reported stimulation of the insula in 5 cases, which resulted in 19 different responses[354], including feeling of nausea, sensations or pain in umbilicus or epigastrium, rising epigastric sensations, tastes, sensations in stomach (ipsilateral), costal region (contralateral) and contralateral arm. In the 1970s, Ojemann and Whitaker[355] found evidence of the involvement of the left insula in speech, based on intraoperative electrical mapping of its cortex. The use of insular cortex stimulations was, however, interrupted for decades due to concerns about the safety of electrode implantations in this area, as the insular cortex is densely populated with blood vessels in the lateral fissure. This changed in the late 1990s, when the safety of trans-opercular stereotactic implantation of electrodes in the insula could be demonstrated[356–358].

Over the last twenty years, the open cortical mapping of the insula has been explored by various groups globally[323,332,334,359–367], including Nguyen et al[368] in Canada who reported insular cortex recordings in nine patients prior to extensive cortical resections for therapy-resistant epilepsy. Clinical responses were elicited in 78% of patients (seven out of nine). In the context of chronic and therapy-resistant epilepsy and the potential for plastic remodeling of cortical functions, these responses should be interpreted with caution. Somatosensory symptoms were encountered in 62% of all elicited responses (such as numbing, tingling, warmth, electric or airflow sensations), mostly contralaterally (primarily when the limbs were involved) but also bilaterally (in a significant number). Additionally, visceral symptoms (12%, such as nausea, abdominal buzz, or rising warmth sensation in the digestive system),

motor symptoms (12%), and auditory symptoms (9%) were found. Vertigo (3%) or speech arrest (3%) were rare.

In a retrospective analysis of 669 stimulations in 222 patients who were admitted for presurgical stereo-electro-encephalography, Mazzola et al. [356] from the group of Lyon, France, found that 550 stimulations of the insular cortex were clinically eloquent (with more than 80% evoking a response). This is the largest series of stimulations of the human insular cortex to date. The most frequent responses were somatosensory (61% of evoked sensations, including pain) and visceral sensations (14.9%), followed by auditory sensations (8%), vestibular illusions (7.5%), speech impairment (5%), gustatory (2.7%) and olfactory (1%) sensations. Pain sensation were dominantly elicited in the posterosuperior insular quadrant, leading Mazzola et al. to conclude that "the exceptional abundance of insular responses to stimulations, of which more than 80 % are clinically eloquent (…) suggests that the insular cortex is one of the most eloquent cortical regions. Furthermore, the diversity of evoked symptoms is such that the insular cortex is likely to contribute to integration of multimodal inputs."

Interpreting data collected in the context of epilepsy must be taken with caution, as the "epileptic" insula may be differently reorganized than the "physiological" insula. Pugnaghi et al. presented an elegant study in 2011[362] that separated the results of stimulations of the "epileptic" from the "physiological" insula. The stimulation of the "epileptic" insula showed, besides seizures, almost only somatosensory manifestations, in contrast to the various responses found in the "physiological" insula. In the "physiological" insula, high-frequency stimulation of the insular cortex induces approximately 80% of responses, of which approximately 70 % were somatosensory, 8% motor, 8% auditory, 2% involved speech, 1% visceral and 1% gustatory (10% other). These results were generally consistent with the studies mentioned above. Rachidi et al.[369] compared the results of seven major insular cortex stimulation studies[323,356,359,361–363,368] in 2021. Viscerosensitive manifestations were elicited in 1 up to 53% of stimulations, visceromotor (0-16%), somatosensory (28%-69%), gustatory (0-13%), olfactory (0-3%), auditory (0-13%), vestibular (0-8%), speech (0-12%), motor (0-16%) and others (0-6%).

The anatomy of the insula had not been fully reexamined since the seminal studies of the 1960s and 1980s, and these earlier studies served as a foundation for relating functional and connectivity studies in monkey.

Our contribution to the understanding of the insular cortex includes two papers[370,371]. The first paper, "The Insula of Reil Revisited: Multiarchitectonic Organization in Macaque Monkeys" [371] aimed to reappraise the anatomical organization of the insula and its boundaries with opercular areas in macaque monkey, using a multiarchitectonic approach based on the distribution of the calcium-binding protein parvalbumin (PV), the non-phosphorylated neurofilament protein (with SMI-32), and acetylcholinesterase (AChE), in addition to Nissl and myelin staining. The combination of these markers has been useful in defining cortical and subcortical areas [372] and their distribution in the insula and adjacent opercula, and should provide a new foundation for relating functional (physiological) and connectional studies in monkeys. This "revisiting" of the multiarchitectonic organization of the insula in monkey is expected to provide a framework for future investigations into the functional (electrophysiological) and connectional aspects of the insula in primates, as well as for comparative studies in different primate species, including humans.

In a cooperation between the universities of Zürich and Fribourg, the brains of 13 monkeys used in previous experiments [373–376] were reexamined. Additional series of free-floating histological sections were stained for myelin and AChE. Unfolded maps of the insular cortex and fronto-parietal and temporal opercula were drawn using a Leica (DM 6000B) microscope equipped with a digital camera and a computerized system (Neurolucida). The architectonic borders were independently assessed by a least two investigators, and most congruent borders were considered reliable.

The major findings of this research on the multi-architectonic organization of the monkey's insula were as follows: the presence of several additional subdivisions within the major classic cytoarchitectonic insular domains (Ia, Id and Ig); the definition of an insula proper with distinct immunohistochemical patterns from the rest of the morphological insula; and the intrusion of orbitofrontal gustatory, parietal somatosensory, and temporal auditory cortical areas into the dorsal, ventral and posterior morphological insula. With this contribution, we aimed to provide a new basis for relating functional (physiological) and connectional studies in monkeys.

Since its publication, this contribution has been cited 60 times.

Given the fragmented current knowledge of the microanatomical organization of the human insula, a second study[370] ("The human insula: architectonic organization and postmortem MRI registration") was conducted to provide detailed unfolded cytoarchitectonic maps. The study used a similar approach as in monkeys, utilizing human post-mortem brain specimens. In addition, post-mortem high resolution MR imaging acquisition was obtained prior to histological processing. The distribution of Von Economo neurons (VENs) in the anterior part of the insula was also studied, as these neurons are thought to play a role in decision making, complex social cognition, and self-awareness[335,377,378].

The study utilized four post-mortem human brain specimens. MR imaging was performed on 3.0 or 7.0 Tesla systems in three of the four brains. Insular blocks were processed and stained for Nissl and Cresyl-Violet myelin, as well as immune-stained for calcium-binding protein parvalbumin (PV). Histological material was analyed with the assistance of a Leica (DM 6000) microscope equipped with a digital camera and computerized plotting system (Neurolucida). Unfolded maps of the insula were created using a similar approach as in the first study on monkeys, based on Nissl staining and correlated with additional staining techniques (myelin and parvalbumin). The cytoarchitectonic organization was related to the insular surface landmarks identified using high-resolution stereotactic MRI of the same brains.

Major findings and conclusions of the study: The unfolding of insula maps confirmed the overall cytoarchitectonic gradients as proposed by Mesulam, ranging from the posterodorsal granular cortex to the middle dysgranular and anteroventral agranular cortex. The relative proportions of these cytoarchitectonic domains were compared to those measured in the insula of monkeys. The major difference is that the dysgranular (Id) domain on average covers half the territory in the human insula, whereas in monkeys it covers only one-third. The human insula shows a reduction in the granular (G and Ig) domains and an increase (by approximately twofold) in the aganular domain compared to monkeys. This increase in the dysgranular domain in the human insula could be related to the significant expansion of multimodal, associative cortex and their interactions with the insula.

The relationship between cytoarchitectonic parcellation and myeloarchitecture and PV immunostaining was similar to that in monkeys. Interestingly, the zone of densest PV is discontinuous in the dorsal insula, with a separate area at mid-dorsal level. This area as been associated with sensory processing, in particular pain, but is also considered as the primary

human taste area[321]. Stimulations of this region evoked viscerosensations, including gustation[323]. It resembles the PV-rich area in the anterior insula of the monkey, and the "shift" to more posterior locations in humans was suggested to be related to the specific development of the anterior insula. Neuroimaging studies show quite different activation patterns depending on the taste stimulus, but the sensitivity of this presumed primary taste area to oral touch, texture, and temperature goes along with a more "sensory," thalamic afferented hypergranular and PV-dense cortex, as it is the case in our study. A reversal in cytoarchitectonic gradients occurs at the junction with the temporal operculum (pointing to a boundary with auditory cortex) and in the anterior insula, at the border with the orbitofrontal cortex.

Our data confirm the overall distribution of VENs in the anterior insula. In addition, these neurons were found to occupy a large territory extending into dysgranular fields (Id1 and Id2). The presence of VEN's in the dysgranular field may have a role in strengthening cognitive-emotional interactions in humans. The larger size of the agranular and more extensive distribution of VENs in the human insula compared to that of monkeys suggests, as proposed by Nieuwenhuys[324], that the human anterior insula has expanded and "specialized" rather than being a "newly evolved" area unique to hominoids. No obvious lateralization was found in the distribution of VEN's. The VENs in the anterior insula and anterior cingulate cortex, two closely interconnected paralimbic areas, are proposed to be important in the neural circuitry underlying social awareness[378]. Loss or dysmorphias of VENs have been found in frontotemporal dementia, a clinical state affecting social awareness, self-control, and empathy. Changes in the VENs density or morphology have been found in autism, corpus callosum agenesis, and schizophrenia[347,348,350,379]. Projections of cytoarchitectonic maps onto sagittal MRIs demonstrate that each major domain extends across several insular gyri, with the largest territory devoted to the dysgranular domain spreading over all gyri. The position of stereotactic planes in relation to topographical gyral and sulcal patterns is quite comparable across cases, despite differences in overall brain morphology. This study provides a framework for future complementary multi-architectonic studies of the human insula and 3D MRI registrations to improve integration into in vivo MR imaging and clinical applications.

This second contribution has been cited 108 times since its publication in 2013.

General conclusion:

In the first section, we demonstrated a high targeting accuracy and a low side-effect profile of MRgFUS compared to other techniques involving cerebral penetration. With a targeting accuracy of within one millimeter and the absence of brain shift, the technique eliminates the need for reversible therapeutic energy application and reduces the risk of placing a thermolesion away from the intended target.

In the second section, we proposed a refined approach to MRgFUS PTT in PD, taking into account interindividual variability, and showed its reproducibility in 31 and later 56 interventions. The safety and efficacy of MRgFUS PTT was evaluated in 51 consecutive patients, with a median follow-up of 12 months, and 15 patients treated bilaterally. The clinical results showed that postoperative scores off-medication improved by 84% for tremor, 70% for rigidity, and 73% for distal hypobradykinesia for the treated side, compared to preoperative scores on-medication. The study also found a strong reduction in pain, dyskinesia, dystonia, and REM sleep disorders, and a 55 % reduction in mean L-DOPA intake. There were no serious adverse events reported, including no bleeding, infection, or ballism. In the fourth article, ten patients who received bilateral MRgFUS PTT were followed up for one year, and the results showed a 52% reduction in mean total UPDRS score off-medication, compared to baseline scores on-medication, thus showing the impact of surgery on PD symptoms. Tremor was reduced by 91%, distal rigidity 67% and distal hypobradykinesia 54%. Dyskinesia were suppressed in 4 out of 4 patients, dystonia in 4 out of 5, and sleep disorders in 3 out of 4. There was a 89% reduction in mean subjective pain, and the mean L-DOPA intake was reduced from 690 mg to 110 mg per day. Axial items, including postural instability and gait, showed only slight improvement, but this was not statistically significant. However, speech difficulties increased by 58%.

The results of chronic and therapy-resistant PD, although extracted from retrospective analysis, suggest a strong efficacy of MRgFUS PTT and particularly bilateral PTT in controlling symptoms such as tremor, distal rigidity, distal hypobradykinesia, dyskinesias, dystonia, and pain compared to best medical treatment at baseline. The stability of symptom control over time after MRgFUS PTT has not been demonstrated yet, but our present daily routine, with all patients being controlled personally monitored by the author of this manuscript, allows us to be confident about its stability over time (personal observation).

Many patients from the first clinical study have now reached 3 and even 5 years of follow-up examination and have not shown worrisome symptom recurrences.

The challenge posed by bilateral PTT surgery currently lies in speech. However, it does not affect every patient in the same way or to the same extent, and improvements (not yet quantified) are seen on follow-up exams. These difficulties seem to primarily concern hypophonia, rather than dysarthria. Our hypotheses for these speech difficulties are discussed in the two clinical papers. Capsular involvement seems to be clearly ruled out based on all postoperative MR examinations. Devices like the EMST150 (expiratory muscle trainer) have shown some promising results over the last 2 years. The issue of speech and speech therapy must be addressed with patients and their families prior to bilateral PTT.

The issue of speech will be central for the future of stereotaxy in PD. Chronic stimulation of the subthalamic nucleus has also been shown to cause speech worsening in up to 69% of patients. As gait, postural stability, and other axial functions did not significantly improve, surgery, as it has been well recognized since years, should only be offered very restrictively if these symptoms are dominant.

A slowing down of psychomotricity has been observed in older patients on longer follow-ups. This observation is difficult to assess with scoring systems in PD and part of this general impression could be due to the normal aging process. After the suppression of a strong tremor in all four extremities, a patients will indeed appear exceptionally quiet to the examiner. This issue of slowing down or stepping back and becoming quieter is seen regularly in older patients. It has been discussed, among other problems, by Professor Agid[380] in the context of DBS surgery. Younger patients (below 60 years) did not show such developments.

In section three, the safety and efficacy of unilateral, and in three cases bilateral, MRgFUS CTT for ET were examined. In a second step, a refined targeting strategy was proposed after histological re-appraisal of the CTT target. The technical feasibility and clinical results were demonstrated in 10 consecutive cases with one-year follow-up. Tremor control improved from 70 % in the first study to over 90 % in the second contribution. The efficacy and global risk profile of this refined targeting strategy need to be demonstrated in larger series and later replicated by others to be validated. We believe this approach is clearly superior to ventral VLp (Vim) thalamotomy, with higher tremor relief and fewer side-effects (mainly paresthesia). Our preliminary bilateral MRgFUS CTT data show slight to moderate difficulties of speech, affecting around 60% of patients, mostly with slight intensity. It

concerns articulation sharpness, which can considered a mild form of dysarthria. These data will need to be critically compared with bilateral MRgFUS thalamotomies of comparable efficacy on tremor control (which are currently lacking). The debate between Vim or PSA DBS (posterior subthalamic area, including the cerebellothalamic tract) is still ongoing, but seems to favor PSA DBS as proposed by Blomstedt et al.[381–383].

In section four, a re-appraisal of the anatomical organization of the insula and its boundaries in macaque monkey, as well as its neighboring opercular areas, was proposed using a multiarchitectonic approach. The second article included unfolded maps of the cytoarchitectonic boundaries of the human insula and projections on their corresponding stereotactic MR images, providing a new anatomical basis for clinical applications and functional imaging studies of the human insula.

Prospects

The incisionless MR-guided focused ultrasound technique has the potential to revolutionize the field of stereotactic functional neurosurgery, with its high targeting accuracy and low rate of technique-related side effects. The clinical efficacy will depend on proper patient selection, target choice, optimized target identification/localization, and optimized thermolesional target coverage. The duration of MRgFUS interventions has been reduced from over 12 hours in 2008 to 2-3 hours, including stereotactic frame fixation and intra- and postoperative imaging. This allows even older and frailer patients to tolerate the procedure without sedation. Over the past five years, no patient at our institution have had to stay hospitalized for more than one night due to a postoperative surgical complication. Given the past COVID-19 pandemic, the “semi-ambulatory” nature of this kind of intervention will be highly welcomed in overcrowded hospitals.

The issue of bilateral treatments, not only in PD but also in ET, will be of great significance in challenging the dominance of the DBS technique in the field of functional neurosurgery. The general feasibility of bilateral lesioning has been demonstrated in the past, but larger patient populations with longer follow-up periods still need to be published in order to fully establish staged bilateral MRgFUS as the first-choice treatment for PD and ET.

The application of preoperative high-resolution 7 Tesla MR imaging, which currently being investigated at various institutions in our country, such as ETH Zürich and the University of Bern, has the potential to improve target identification through direct visualization and thus potentially reduce the necessary target coverage volume to control symptoms. This could be used not only for fibre tracts in the subthalamus but also for nuclear targets, such as the Central Lateral nucleus and the Centre Médian thalamotomies.

Data on bilateral ET treatments, which have been systematically collected over the past 5 years, should be published, as well as a large retrospective series on MRgFUS for treating neuropathic pain conditions. In the context of the opioid crisis in the United States, it is important to collect data on alternative treatments, as we believe that opioids not only fail to help, but are actually detrimental in treating neuropathic pain.

The neuropsychological outcomes after bilateral PTT surgery will need to be studied again in cooperation with a university to exclude or demonstrate any mental difficulties that may have been missed with our basic assessment tools, such as Montreal Cognitive Assessment (MoCA) and patient and relatives interviews.

Quantitative EEG examinations have been performed on every patient who has undergone MRgFUS surgery at the centre of ultrasound functional neurosurgery in Solothurn. These most valuable and unique data (pre- and postoperative) will also need to be systematically analyzed for postoperative changes as well as disease characterisation, as they had been in the past, but with large number of patients[384–389].

We believe that the full potential of MRgFUS has not yet been realized. As a first step, it is necessary to re-explore the field of chronic and therapy-resistant neurological disorders, such as dystonia, tinnitus, epilepsy, narcolepsy, and neuropsychiatry, in order to provide patients with better symptom relief than what is currently possible with conventional treatments. There is already valuable data from both the older and recent literature, but it needs to be revisited using more modern tools. For neuro-oncological and neurovascular applications, the use of FUS is at its early stages and significant breakthrough are expected, given sufficient investment in our institutions.

The surgical management of PD, regardless of the technique used, would greatly benefit from integrated psychotherapy, both before and especially after functional neurosurgical interventions. We believe that many patients could indeed benefit from a humanistic psychotherapeutic support. Even if the motor symptoms and, to a lesser extent, the non-motor symptoms can disappear after MRgFUS, the disease concept itself often remains very vivid, even years after treatment and a positive evolution without the appearance of any recurring or new symptoms.

In the field of movement disorders, the next pathology that could be treated with MRgFUS is dystonia, which is the third most common movement disorder after ET and PD. Among all forms of dystonia, cervical dystonia is the most frequent and is likely underdiagnosed, with a possible prevalence of above 0.4% in the general population[390,391]. This means there are at least 3’000 patients in Switzerland alone and over 3 million cases worldwide[392]. According to Balint et al, about 20% of patients in a movement disorder clinic suffers from some form of dystonia. The overall prevalence of all dystonia syndromes is probably around 0.7%. In an elderly population (Bruneck Study cohort, 50-89 years), Wenning et al.[393] found that movement disorders had a prevalence of 28%. Tremor was found in 14.5%, followed by restless legs syndrome (10.8%), parkinsonism (7%) and dystonia (1.8%).

According to the consensus update by Albanese and coworkers[394], “Dystonia is a movements disorder characterized by sustained or intermittent muscle contractions causing abnormal,

often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation." The modern classification of dystonia is based on two axes: one taking into account clinical characteristics, and the other, the etiology of the disease. Based on its body distribution, a dystonia can be focal, segmental, multifocal, generalized, or limited to one side of the body (hemi-dystonia). The temporal pattern, age of onset, and associated features are also considered. The etiology separates structural lesions, degeneration, or a lack of evidence for either. Additionally, inherited forms are differentiated from acquired or idiopathic forms. The term "dystonia" can be refer to a single sign or disease in which dystonia is the sole or prominent clinical feature. Previous classifications focused on etiology and characterized dystonia as primary or secondary. This categorization remains useful, especially when considering invasive neurosurgical approaches.

The clinical syndromes and etiologies of dystonia largely overlap, making it difficult to develop a unifying clinical and pathophysiological conceptualization. Over the years, several models of dystonia have been proposed, with the most useful ones studied in sub-human primates. Evidence suggests that the basal ganglia for playing a major role in dystonia, although other systems may also be involved[395]. According to the various models of dystonia, all structures of the basal ganglia, including the striatum, have been found to be either overactive or inhibited, depending on the study and the type of dystonia[396–402]. Relevant methodological confounding factors may have contributed to the somewhat confusing literature on the pathophysiology of dystonia. For example, propofol anesthesia has been found to strongly reduce the bursting frequency of both the GPe and GPi[403]. Lesions have mostly been found in the striatum, but also in the pallidum, and electrophysiologically measured overactivity has been documented[404].

In our view, it is important to consider two distinct categories when looking at surgical treatment for dystonia from a pathophysiological. The category consists of primary dystonia and task-related dystonia, and the second category encompasses secondary dystonia, which is characterized by morphological lesions. For the first category, we hypothesize that overactivity in the striatum leads to reduced activity in the GPe and increased activity in the GPi, which is similar to the situation seen in PD. Surgical procedures such as posteroventral pallidotomy, thalamotomy, or posteroventral thalamotomy have been successful in treating primary and task-related dystonia in the past[405,406].

In contrast, secondary dystonia is thought to be more challenging to control surgically. A "simple" internal pallidotomy or PTT may not be sufficient in these cases, and a more complex approach may be needed. We believe that combining these procedures with external pallidotomy or nucleus subthalamotomy may improve the outcome by directly or indirectly controlling an overactive pallido-reticular pathway to the thalamus. Evidence for this projection in humans is present, but still very limited in the literature[407].

In our opinion, two central questions must be answered before considering a functional neurosurgical approach; 1) Where is the lesion or source of the overactivity and 2) Is the neuronal network locked in an overactivity that the brain cannot compensate for on its own or with the use of any drugs.

The first surgical experiences applying the MRgFUS in chronic and therapy-resistant dystonia focused, as we strongly believe it should have, on focal dystonia. The Tokyo group, led by neurosurgeons Drs Takaomi Taira and Shiro Horisawa, published their early and promising experiences using MRgFUS to treat dystonia in 2018 and 2021[117,118]. Their experience with the RF technique dates back a long time and still ongoing[406,408,409].

While the DBS technique continues to dominate the field of therapy-resistant dystonia, we believe there is a pressing need to develop a safe and efficient alternative neurosurgical treatment, as many patients are very hesitant to undergo interventions involving implants within their brains.

Acknowledgements

My thanks go to my family, who have always supported me throughout my life with their trust and kindness.

I am very deeply indebted to all my former teachers, especially Dr. Morel, who trusted me very early on and shared her vast knowledge, anecdotes of a life of research, her deep scientific ethics, and respect for meticulous work. Professor Jeanmonod, a bottomless well of knowledge, also trusted me very early on and imparted so much to me over the last 17 years, 8 of which were spent in the next-door office. He embodies perseverance at its best, despite the vagaries of life and fashion.

I would also like to express my gratitude to my department heads during my neurosurgical residency, Professors Gerhard Hildebrandt and Karl Schaller and Dr Martin Baur. Professor

Hildebrandt set an example of calmness, education, reliability and benevolence in addition to his unfailing support, which remains a source of inspiration to this day.

A special thanks to my colleagues at SoniModul, Dr. Anouk Magara, David Moser and Franziska Rossi, as well as to all the chief residents and residents with whom I have shared most of my days during the last 15 years.

I am finally very grateful to Professor Gregor Rainer and Drs. Melanie Kaeser and Ivan Cabrilo for their constructive comments in finalizing this manuscript. My thanks also go to the spelling correction programs Word (Microsoft), deepl.com and chat.openai.com which I hope have helped to reduce the language inaccuracies in this manuscript.

References

1. Martin, E., Jeanmonod, D., Morel, A., Zadicario, E. & Werner, B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Ann. Neurol.* **66**, 858–861 (2009).
2. Jeanmonod, D. *et al.* Transcranial magnetic resonance imaging–guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus* **32**, E1 (2012).
3. Moser, D., Zadicario, E., Schiff, G. & Jeanmonod, D. Measurement of targeting accuracy in focused ultrasound functional neurosurgery. *Neurosurg Focus* **32**, E2 (2012).
4. Moser, D., Zadicario, E., Schiff, G. & Jeanmonod, D. MR-guided focused ultrasound technique in functional neurosurgery: targeting accuracy. *J Ther Ultrasound* **1**, 3 (2013).
5. Magara, A. *et al.* First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound* **2**, 11 (2014).
6. Gallay, M. N., Jeanmonod, D., Liu, J. & Morel, A. Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery. *Brain Struct Funct* **212**, 443–463 (2008).
7. Morel, A. *Stereotactic Atlas of the Human Thalamus and Basal Ganglia*. (CRC Press, New York, 2007).
8. Gallay, M. N., Moser, D., Federau, C. & Jeanmonod, D. Anatomical and technical reappraisal of the pallidothalamic tractotomy with the incisionless transcranial MR-guided focused ultrasound. A technical note. *Front Surg* **6**, (2019).
9. Gallay, M., Moser, D., Federau, C. & Jeanmonod, D. Radiological and thermal dose correlations in pallidothalamic tractotomy with MRgFUS. *Front Surg* (2019).
10. Gallay, M. N. *et al.* MRgFUS Pallidothalamic Tractotomy for Chronic Therapy-Resistant Parkinson's Disease in 51 Consecutive Patients: Single Center Experience. *Front. Surg.* **6**, (2020).
11. Gallay, M. N., Moser, D., Magara, A. E., Haufler, F. & Jeanmonod, D. Bilateral MR-guided focused ultrasound pallidothalamic tractotomy for Parkinson's disease with one year follow-up. *Front. Neurol.* **12**, (2021).
12. Mundinger, F. Die Subthalamotomie zur Behandlung extrapyramidaler Bewegungsstörungen. *Dtsch med Wochenschr* **90**, 2002–2007 (1965).
13. Spiegel, E. A. *et al.* Campotomy in various extrapyramidal disorders. *J. Neurosurg.* **20**, 871–884 (1963).
14. Aufenberg, C. *et al.* A revival of Spiegel's campotomy: long term results of the stereotactic pallidothalamic tractotomy against the parkinsonian thalamocortical dysrhythmia. *Thalamus & Related Systems* **3**, 121–132 (2005).
15. Magnin, M., Jeanmonod, D., Morel, A. & Siegemund, M. Surgical control of the human thalamocortical dysrhythmia:: II. Pallidothalamic tractotomy in Parkinson's disease. *Thalamus & Related Systems* **1**, 81–89 (2001).
16. Gallay, M. N. *et al.* Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J Ther Ultrasound* **4**, 5 (2016).
17. Gallay, M. N., Moser, D. & Jeanmonod, D. MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. *J Neurosurg* 1–10 (2020).
18. Meyers, R. Dandy's striatal theory of the center of consciousness; surgical evidence and logical analysis indicating its improbability. *Trans Am Neurol Assoc* **51**, 44–49 (1950).
19. Spiegel, E. A., Wycis, H. T., Marks, M. & Lee, A. J. Stereotaxic Apparatus for Operations on the Human Brain. *Science* **106**, 349–350 (1947).
20. Horsley, V. & Clarke, R. H. The structure and functions of the cerebellum examined by a new method. *Brain* **31**, 45–124 (1908).
21. Kandel, E. I. *Functional and Stereotactic Neurosurgery*. (Springer, New York, 1989).

22. Zernov, D. L'encéphalomètre. *Rev Gen Clin Ther* 19:302 (1892).
23. Fodstad, H., Hariz, M. & Ljunggren, B. History of Clarke's stereotactic instrument. *Stereotact Funct Neurosurg* **57**, 130–140 (1991).
24. Hoffman, L. A. & Vilensky, J. A. Encephalitis lethargica: 100 years after the epidemic. *Brain* **140**, 2246–2251 (2017).
25. Krusz, J. C., Koller, W. C. & Ziegler, D. K. Historical review: Abnormal movements associated with epidemic encephalitis lethargica. *Movement Disorders* **2**, 137–141 (1987).
26. Cotzias, G. C., Van Woert, M. H. & Schiffer, L. M. Aromatic amino acids and modification of parkinsonism. *N. Engl. J. Med.* **276**, 374–379 (1967).
27. Andy, O. J., Jurko, M. F. & Sias, F. R. Subthalamotomy in treatment of parkinsonian tremor. *J Neurosurg* **20**, 860–870 (1963).
28. Bertrand, C., Martinez, S. N., Hardy, J., Molina-Negro, P. & Velasco, F. Stereotactic Surgery for Parkinsonism. **5**, 79–112 (1973).
29. Bertrand, C., Hardy, J., Molina-Negro, P. & Martínez, N. Optimum physiological target for the arrest of tremor. in *Third Symposium on Parkinson's Disease. Edinburgh, Livingstone* 251–259 (1969).
30. Bravo, G., Mata, P. & Seiquer, G. Surgery for bilateral Parkinson's disease. *Confin Neurol* **29**, 133–138 (1967).
31. Bravo, G., Parera, C. & Seiquer, G. Neurological side-effects in a series of operations on the basal ganglia. *J. Neurosurg.* **24**, 640–647 (1966).
32. Cooper, I. S. Cryogenic technique of thalamic surgery for parkinsonism and other involuntary movement disorders. in *Progress in Neurological Surgery* vol. 5 159–188 (Karger Publishers, 1973).
33. Cooper, I. S. *Parkinsonism: Its Medical and Surgical Therapy.* (Springfield, Illinois: Thomas, 1961).
34. Cooper, I. S. & Bravo, G. Chemopallidectomy and chemothalamectomy. *J. Neurosurg.* **15**, 244–250 (1958).
35. Cooper, I. S. Neurosurgical alleviation of intention tremor of multiple sclerosis and cerebellar disease. *N Engl J Med.* **263**, 441–444 (1960).
36. Fenelon, F. Essai de traitement neurochirurgical du syndrome parkinsonien par intervention directe sur les voies extrapyramidales (anse lenticulaire). *Rev. neurol.* **83**, 437–440 (1950).
37. Gillingham, F. J., Kalyanaraman, S. & Donaldson, A. A. Bilateral stereotaxic lesions in the management of parkinsonism and the dyskinesias. *Br Med J* **2**, 656–659 (1964).
38. Guiot, G. & Brion, S. Traitement neuro-chirurgical des syndromes choréo-athétosiques et parkinsoniens. *Sem Hop Paris* **28**, 2095–2099 (1952).
39. Hassler, R., Mundinger, F. & Riechert, T. Correlations between clinical and autoptic findings in stereotaxic operations of parkinsonism. *Confin Neurol* **26**, 282–290 (1965).
40. Hécaen, H., Talairach, J., David, M. & Dell, M. B. Coagulations limitées du thalamus dans les algies du syndrome thalamique. Résultats thérapeutiques et physiologiques. *Revue Neurologique* **81**, 917–931 (1949).
41. Jinnai, D. & Mukawa, J. Forel-H-tomy for the treatment of epilepsy. *Confin Neurol* **32**, 307–315 (1970).
42. Krayenbuhl, H., Akert, K., Hartmann, K. & Yasargil, M. G. Study of the anatomo-clinical correlation in patients operated on for parkinsonism. *Neurochirurgie* **10**, 397–412 (1964).
43. Krayenbühl, H., Wyss, O. A. & Yasargil, M. G. Bilateral thalamotomy and pallidotomy as treatment for bilateral parkinsonism. *J. Neurosurg.* **18**, 429–444 (1961).
44. Mark, V. H. & Hackett, T. P. Surgical aspects of thalamotomy in the human. *Trans Am Neurol Assoc* **84**, 92–94 (1959).
45. Meyers, R. Surgical interruption of the pallidofugal fibers. Its effect on the syndrome of paralysis agitans and technical considerations in its application. *NY State J Med* **42**, 317–325 (1942).

46. Mundinger, F. Stereotaxic Interventions on the Zona Incerta Area for Treatment of Extrapyramidal Motor Disturbances and their Results. *Stereotact Funct Neurosurg* **26**, 222–230 (1965).
47. Mundinger, F. & Riechert, T. The stereotactic brain operations for the treatment of extrapyramidal movement disorders (parkinsonism and hyperkinesias) and their results. *Fortschritte der Neurologie, Psychiatrie, und ihrer Grenzgebiete* **31**, 69 (1963).
48. Narabayashi, H. & Okuma, T. Procaine-oil blocking of the globus pallidus for the treatment of rigidity and tremor of parkinsonism (preliminary report). *Proceedings of the Japan Academy* **29(3)**, 134–137 (1953).
49. Narabayashi, H., Okuma, T. & Shikiba, S. Procaine oil blocking of the globus pallidus. *AMA Arch Neurol Psychiatry* **75**, 36–48 (1956).
50. Riechert, T. Long term follow-up of results of stereotaxic treatment in extrapyramidal disorders. *Confin Neurol* **22**, 356–363 (1962).
51. Siegfried, J. Stereotactic pulvinarotomy in the treatment of intractable pain. in *Pain-Its Neurosurgical Management* vol. 8 104–113 (Karger Publishers, 1977).
52. Talairach, J. & Szikla, G. Application of stereotactic concepts to the surgery of epilepsy. *Acta Neurochir Suppl (Wien)* **30**, 35–54 (1980).
53. Talairach, J., Tournoux, P., Musolino, A. & Missir, O. Stereotaxic exploration in frontal epilepsy. *Adv Neurol* **57**, 651–688 (1992).
54. Wycis, H. T. & Spiegel, E. A. Ansotomy in paralysis agitans. *Confin Neurol* **12**, 245–246 (1952).
55. Yasargil, M. G., Wyss, O. A. & Krayenbuhl, H. [Study on treatment of extrapyramidal diseases by aimed brain surgery; report on 75 individual cases]. *Schweiz Med Wochenschr* **89**, 143–150 (1959).
56. Meyers, R. The surgery of the hyperkinetic disorders. *in Vinken PJ, Bruyn GW (eds): Diseases of the Basal Ganglia. New York, North-Holland Publishing, 1968, pp 844– 878.* (1968).
57. Rolston, J. D., Englot, D. J., Starr, P. A. & Larson, P. S. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: Analysis of multiple databases. *Parkinsonism & Related Disorders* (2016) doi:10.1016/j.parkreldis.2016.09.014.
58. Oh, M. Y., Abosch, A., Kim, S. H., Lang, A. E. & Lozano, A. M. Long-term hardware-related complications of deep brain stimulation. *Neurosurgery* **50**, 1268–1276 (2002).
59. Leksell, L. Stereotactic radiosurgery. *J Neurol Neurosurg Psychiatry* **46**, 797–803 (1983).
60. Duma, C. M. *et al.* Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five-year experience. *J. Neurosurg.* **88**, 1044–1049 (1998).
61. Duma, C. M., Jacques, D. & Kopyov, O. V. The treatment of movement disorders using Gamma Knife stereotactic radiosurgery. *Neurosurg. Clin. N. Am.* **10**, 379–389 (1999).
62. Friedman, D. P., Goldman, H. W., Flanders, A. E., Gollomp, S. M. & Curran, W. J. Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation--preliminary experience. *Radiology* **212**, 143–150 (1999).
63. Friedman, J. H. *et al.* Gamma knife pallidotomy in advanced Parkinson's disease. *Ann. Neurol.* **39**, 535–538 (1996).
64. Kooshkabadi, A., Lunsford, L. D., Tonetti, D., Flickinger, J. C. & Kondziolka, D. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. *J. Neurosurg.* **118**, 713–718 (2013).
65. Lim, S.-Y. *et al.* Gamma knife thalamotomy for disabling tremor: a blinded evaluation. *Arch. Neurol.* **67**, 584–588 (2010).
66. Lovo, E. E. *et al.* Stereotactic Gamma Ray Radiosurgery to the Centromedian and Parafascicular Complex of the Thalamus for Trigeminal Neuralgia and Other Complex Pain Syndromes. *Cureus* **11**, (2019).
67. Mathieu, D., Kondziolka, D., Niranjan, A., Flickinger, J. & Lunsford, L. D. Gamma knife thalamotomy for multiple sclerosis tremor. *Surg Neurol* **68**, 394–399 (2007).

68. Niranjan, A., Jawahar, A., Kondziolka, D. & Lunsford, L. D. A comparison of surgical approaches for the management of tremor: radiofrequency thalamotomy, gamma knife thalamotomy and thalamic stimulation. *Stereotact Funct Neurosurg* **72**, 178–184 (1999).
69. Niranjan, A., Raju, S. S. & Lunsford, L. D. Leksell Radiosurgery for Movement Disorders. *Prog Neurol Surg* **34**, 279–288 (2019).
70. Ohye, C., Shibazaki, T., Ishihara, J. & Zhang, J. Evaluation of gamma thalamotomy for parkinsonian and other tremors: survival of neurons adjacent to the thalamic lesion after gamma thalamotomy. *J. Neurosurg.* **93 Suppl 3**, 120–127 (2000).
71. Pan, L. *et al.* Stereotactic Gamma thalamotomy for the treatment of parkinsonism. *Stereotact Funct Neurosurg* **66 Suppl 1**, 329–332 (1996).
72. Raju, S. S., Niranjan, A., Monaco, E. A., Flickinger, J. C. & Lunsford, L. D. Stereotactic Radiosurgery for Intractable Tremor-Dominant Parkinson Disease: A Retrospective Analysis. *Stereotact Funct Neurosurg* **95**, 291–297 (2017).
73. Urgosik, D. & Liscak, R. Medial Gamma Knife thalamotomy for intractable pain. *J Neurosurg* **129**, 72–76 (2018).
74. Witjas, T. *et al.* A prospective single-blind study of Gamma Knife thalamotomy for tremor. *Neurology* **85**, 1562–1568 (2015).
75. Young, R. F. *et al.* Gamma knife thalamotomy for treatment of tremor: long-term results. *J Neurosurg* **93**, 128–135 (2000).
76. Young, R. F., Li, F., Vermeulen, S. & Meier, R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. *J Neurosurg* **112**, 1311–1317 (2010).
77. Young, R. F., Li, F., Vermeulen, S. & Meier, R. Gamma Knife thalamotomy for treatment of essential tremor: long-term results. *J Neurosurg* **112**, 1311–1317 (2009).
78. Horisawa, S., Hayashi, M. & Taira, T. Chronic encapsulated expanding hematoma after gamma knife thalamotomy for essential tremor. *World Neurosurgery* (2022) doi:10.1016/j.wneu.2022.01.083.
79. Friehs, G. M. *et al.* Lesion size following Gamma Knife treatment for functional disorders. *Stereotactic and Functional Neurosurgery* **66**, 320–328 (1996).
80. Young, R. F. Functional neurosurgery with the Leksell Gamma knife. *Stereotact Funct Neurosurg* **66**, 19–23 (1996).
81. Jagannathan, J. *et al.* High-intensity focused ultrasound surgery of the brain: part 1—a historical perspective with modern applications. *Neurosurgery* **64**, 201–211 (2009).
82. Dunn, F. & Fry, F. J. Ultrasonic threshold dosages for the mammalian central nervous system. *IEEE Trans Biomed Eng* **18**, 253–256 (1971).
83. Fry, F. J. Precision high intensity focusing ultrasonic machines for surgery. *American Journal of Physical Medicine & Rehabilitation* **37**, 152–156 (1958).
84. Fry, W. J. & Fry, F. J. Fundamental neurological research and human neurosurgery using intense ultrasound. *IRE Trans Med Electron* **ME-7**, 166–181 (1960).
85. Fry, W. J., Fry, F. J., Meyers, R. & Eggleton, R. J. The use of ultrasound in neurosurgery. *Proc. III Intern. Conf. Med. Electron. London* 453–458 (1960).
86. Fry, W. J., Mosberg, W. H., Barnard, J. W. & Fry, F. J. Production of focal destructive lesions in the central nervous system with ultrasound. *J Neurosurg* **11**, 471–478 (1954).
87. Meyers, R. *et al.* Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. *J. Neurosurg.* **16**, 32–54 (1959).
88. Lindstrom, P. A. Prefrontal ultrasonic irradiation—a substitute for lobotomy. *AMA Archives of Neurology & Psychiatry* **72**, 399–425 (1954).
89. Odéen, H., Almquist, S., de Bever, J., Christensen, D. A. & Parker, D. L. MR thermometry for focused ultrasound monitoring utilizing model predictive filtering and ultrasound beam modeling. *J Ther Ultrasound* **4**, (2016).

90. Verius, M., Frank, F., Gizewski, E. & Broessner, G. Magnetic Resonance Spectroscopy Thermometry at 3 Tesla: Importance of Calibration Measurements. *Therapeutic Hypothermia and Temperature Management* **9**, 146–155 (2018).
91. Chang, W. S. *et al.* Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J. Neurol. Neurosurg. Psychiatr.* **86**, 257–264 (2015).
92. Elias, W. J. *et al.* A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus. *J. Neurosurg.* **119**, 307–317 (2013).
93. Elias, W. J. *et al.* A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *N. Engl. J. Med.* **375**, 730–739 (2016).
94. Federau, C. *et al.* Transcranial MRI-guided high-intensity focused ultrasound for treatment of essential tremor: A pilot study on the correlation between lesion size, lesion location, thermal dose, and clinical outcome. *Journal of Magnetic Resonance Imaging* **48**, 58–65 (2018).
95. Halpern, C. H. *et al.* Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. *Neurology* **93**, e2284–e2293 (2019).
96. Harary, M., Segar, D. J., Hayes, M. T. & Cosgrove, G. R. Unilateral Thalamic Deep Brain Stimulation Versus Focused Ultrasound Thalamotomy for Essential Tremor. *World Neurosurgery* **126**, e144–e152 (2019).
97. Schlesinger, I. *et al.* MRI Guided Focused Ultrasound Thalamotomy for Moderate-to-Severe Tremor in Parkinson's Disease. *Parkinsons Dis* **2015**, 219149 (2015).
98. Sinai, A. *et al.* Magnetic resonance–guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. *J Neurosurg* **1**, 1–8 (2019).
99. Zaaroor, M. *et al.* Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J. Neurosurg.* 1–9 (2017) doi:10.3171/2016.10.JNS16758.
100. Zur, G. *et al.* Tremor Relief and Structural Integrity after MRI-guided Focused US Thalamotomy in Tremor Disorders. *Radiology* 191624 (2020).
101. Abe, K. *et al.* Focused Ultrasound Thalamotomy for Refractory Essential Tremor: A Japanese Multicenter Single-Arm Study. *Neurosurgery* **88**, 751–757 (2021).
102. Fukutome, K., Hirabayashi, H., Osakada, Y., Kuga, Y. & Ohnishi, H. Bilateral Magnetic Resonance Imaging-Guided Focused Ultrasound Thalamotomy for Essential Tremor. *Stereotact Funct Neurosurg* 1–9 (2021) doi:10.1159/000518662.
103. Iorio-Morin, C. *et al.* Bilateral Focused Ultrasound Thalamotomy for Essential Tremor (BEST-FUS Phase 2 Trial). *Movement Disorders* **n/a**,.
104. Martínez-Fernández, R. *et al.* Bilateral staged magnetic resonance-guided focused ultrasound thalamotomy for the treatment of essential tremor: a case series study. *J Neurol Neurosurg Psychiatry* **92**, 927–931 (2021).
105. Purrer, V. *et al.* Lesions of the cerebello-thalamic tract rather than the ventral intermediate nucleus determine the outcome of focused ultrasound therapy in essential tremor: A 3T and 7T MRI-study. *Parkinsonism Relat Disord* **91**, 105–108 (2021).
106. Wu, P. *et al.* Focused Ultrasound Thalamotomy for the Treatment of Essential Tremor: A 2-Year Outcome Study of Chinese People. *Front Aging Neurosci* **13**, 697029 (2021).
107. Jameel, A. *et al.* Double lesion MRgFUS treatment of essential tremor targeting the thalamus and posterior sub-thalamic area: preliminary study with two year follow-up. *Br J Neurosurg* 1–10 (2021) doi:10.1080/02688697.2021.1958150.
108. Schreglmann, S. R. *et al.* Unilateral cerebellothalamic tract ablation in essential tremor by MRI-guided focused ultrasound. *Neurology* **88**, 1329–1333 (2017).
109. Jung, H. H. *et al.* Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. *Mol Psychiatry* **20**, 1205–1211 (2015).

110. Bond, A. E. *et al.* Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol* **74**, 1412–1418 (2017).
111. Martínez-Fernández, R. *et al.* Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *Lancet Neurol.* **17**, 54–63 (2018).
112. Na, Y. C., Chang, W. S., Jung, H. H., Kweon, E. J. & Chang, J. W. Unilateral magnetic resonance-guided focused ultrasound pallidotomy for Parkinson disease. *Neurology* **85**, 549–551 (2015).
113. Martínez-Fernández, R. *et al.* Randomized Trial of Focused Ultrasound Subthalamotomy for Parkinson's Disease. *N Engl J Med* **383**, 2501–2513 (2020).
114. Sinai, A. *et al.* Focused Ultrasound Thalamotomy in Tremor Dominant Parkinson's Disease: Long-Term Results. *J Parkinsons Dis* (2021) doi:10.3233/JPD-212810.
115. Yamamoto, K. *et al.* Focused Ultrasound Thalamotomy for Tremor-dominant Parkinson's Disease: A Prospective 1-year Follow-up Study. *Neurol Med Chir (Tokyo)* **61**, 414–421 (2021).
116. Eisenberg, H. M. *et al.* MR-guided focused ultrasound pallidotomy for Parkinson's disease: safety and feasibility. *Journal of Neurosurgery* **1**, 1–7 (2020).
117. Horisawa, S. *et al.* A single case of MRI-guided focused ultrasound ventro-oral thalamotomy for musician's dystonia. *Journal of neurosurgery* **131**, 384–386 (2018).
118. Horisawa, S. *et al.* Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Focal Hand Dystonia: A Pilot Study. *Movement Disorders* (2021).
119. Jamora, R. D. G., Chang, W.-C. & Taira, T. Transcranial Magnetic Resonance-Guided Focused Ultrasound in X-Linked Dystonia-Parkinsonism. *Life (Basel)* **11**, 392 (2021).
120. Lipsman, N. *et al.* MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol* **12**, 462–468 (2013).
121. Zrinzo, L., Foltynie, T., Limousin, P. & Hariz, M. I. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *J. Neurosurg.* **116**, 84–94 (2012).
122. Kantzanou, M., Korfias, S., Panourias, I., Sakas, D. E. & Karalexi, M. A. Deep Brain Stimulation-Related Surgical Site Infections: A Systematic Review and Meta-Analysis. *Neuromodulation: Technology at the Neural Interface* **24**, 197–211 (2021).
123. Prada, F. *et al.* Applications of focused ultrasound in cerebrovascular diseases and brain tumors. *Neurotherapeutics* **16**, 67–87 (2019).
124. Ram, Z. *et al.* Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. *Neurosurgery* **59**, 949–955; discussion 955-956 (2006).
125. McDannold, N., Clement, G. T., Black, P., Jolesz, F. & Hynynen, K. Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery* **66**, 323–332; discussion 332 (2010).
126. Coluccia, D. *et al.* First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound. *J Ther Ultrasound* **2**, 17 (2014).
127. Xu, Z., Hall, T. L., Vlaisavljevich, E. & Lee, F. T. Histotripsy: the first noninvasive, non-ionizing, non-thermal ablation technique based on ultrasound. *International Journal of Hyperthermia* **38**, 561–575 (2021).
128. McDannold, N. J., Vykhodtseva, N. I. & Hynynen, K. Microbubble contrast agent with focused ultrasound to create brain lesions at low power levels: MR imaging and histologic study in rabbits. *Radiology* **241**, 95–106 (2006).
129. Wei, K.-C. *et al.* Focused ultrasound-induced blood-brain barrier opening to enhance temozolomide delivery for glioblastoma treatment: a preclinical study. *PLoS One* **8**, e58995 (2013).
130. Chen, P.-Y. *et al.* Focused ultrasound-induced blood-brain barrier opening to enhance interleukin-12 delivery for brain tumor immunotherapy: a preclinical feasibility study. *J Transl Med* **13**, 93 (2015).

131. Nance, E. A. *et al.* A dense poly(ethylene glycol) coating improves penetration of large polymeric nanoparticles within brain tissue. *Sci Transl Med* **4**, 149ra119 (2012).
132. Mehier-Humbert, S., Bettinger, T., Yan, F. & Guy, R. H. Plasma membrane poration induced by ultrasound exposure: implication for drug delivery. *J Control Release* **104**, 213–222 (2005).
133. Escoffre, J.-M., Novell, A., Serrière, S., Lecomte, T. & Bouakaz, A. Irinotecan delivery by microbubble-assisted ultrasound: in vitro validation and a pilot preclinical study. *Mol Pharm* **10**, 2667–2675 (2013).
134. Kampinga, H. H. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. *Int J Hyperthermia* **22**, 191–196 (2006).
135. Finley, D. S. *et al.* Ultrasound-based combination therapy: potential in urologic cancer. *Expert Rev Anticancer Ther* **11**, 107–113 (2011).
136. Hu, Z. *et al.* Release of endogenous danger signals from HIFU-treated tumor cells and their stimulatory effects on APCs. *Biochem Biophys Res Commun* **335**, 124–131 (2005).
137. Suehiro, S. *et al.* Enhancement of antitumor activity by using 5-ALA-mediated sonodynamic therapy to induce apoptosis in malignant gliomas: significance of high-intensity focused ultrasound on 5-ALA-SDT in a mouse glioma model. *J Neurosurg* **129**, 1416–1428 (2018).
138. Ilyas, A. *et al.* Magnetic resonance-guided, high-intensity focused ultrasound sonolysis: potential applications for stroke. *Neurosurg Focus* **44**, E12 (2018).
139. Gildenberg, P. L. Evolution of Basal Ganglia Surgery for Movement Disorders. *SFN* **84**, 131–135 (2006).
140. Hamani, C. & Lozano, A. M. Hardware-related complications of deep brain stimulation: a review of the published literature. *Stereotact Funct Neurosurg* **84**, 248–251 (2006).
141. Burchiel, K. J., McCartney, S., Lee, A. & Raslan, A. M. Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording: Clinical article. *Journal of Neurosurgery* **119**, 301–306 (2013).
142. Bourgeois, G. *et al.* Accuracy of MRI-guided stereotactic thalamic functional neurosurgery. *Neuroradiology* **41**, 636–645 (1999).
143. Starr, P., Feiwell, R. & Marks Jr, W. Placement of deep brain stimulators into the subthalamic nucleus: technical approach. *Stereotactic and Functional Neurosurgery* **72**, 247–247 (1999).
144. Miller, T. R. *et al.* Predicting final lesion characteristics during MR-guided focused ultrasound pallidotomy for treatment of Parkinson's disease. *Journal of Neurosurgery* **134**, 1083–1090 (2020).
145. Huang, Y. *et al.* Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. *Medical Physics* **45**, 4704–4710 (2018).
146. Gallay, M. N., Moser, D. & Jeanmonod, D. Safety and accuracy of incisionless transcranial MR-guided focused ultrasound functional neurosurgery: single-center experience with 253 targets in 180 treatments. *J Neurosurg* **130**, 1234–1243 (2019).
147. Fishman, P. S. *et al.* Neurological adverse event profile of magnetic resonance imaging–guided focused ultrasound thalamotomy for essential tremor. *Mov Disord.* (2018) doi:10.1002/mds.27401.
148. Kalia, L. V. & Lang, A. E. Parkinson's disease. *Lancet* **386**, 896–912 (2015).
149. von Campenhausen, S. *et al.* Prevalence and incidence of Parkinson's disease in Europe. *Eur Neuropsychopharmacol* **15**, 473–490 (2005).
150. Mtui, E., Gruener, G. & Dockery, P. *Fitzgerald's Clinical Neuroanatomy and Neuroscience E-Book*. (Elsevier Health Sciences, 2020).
151. Parent, A. & Carpenter, M. B. *Carpenter's Human Neuroanatomy*. (Williams & Wilkins, 1996).
152. Strominger, N. L., Demarest, R. J. & Laemle, L. B. *Noback's Human Nervous System: Structure and Function*. (Springer Science & Business Media, 2012).
153. Obeso, J. A. *et al.* Pathophysiology of the basal ganglia in Parkinson's disease. *Trends in Neurosciences* **23**, S8–S19 (2000).

154. Fenelon, F. Bilan de quatre années de pratique d'une intervention personelle pour maladie de parkinson. *Rev. neurol.* **89**, 580–584 (1953).
155. Riechert, T. & Wolff, M. Die technische Durchführung von gezielten Hirnoperationen. *Archiv für Psychiatrie und Nervenkrankheiten* **190**, 297–316 (1953).
156. Cooper, I. S. Ligation of the anterior choroidal artery for involuntary movements; parkinsonism. *Psychiatr Q* **27**, 317–319 (1953).
157. Spiegel, E. A. & Wycis, H. T. Ansotomy in paralysis agitans. *AMA Arch Neurol Psychiatry* **71**, 598–614 (1954).
158. Driollet, R., Schvarcz, J. R. & Orlando, J. Optimum Target for Tremor Arrest. *SFN* **36**, 355–355 (1974).
159. van Manen, J. Stereotactic methods and their applications in disorders of the motor system. (1967).
160. Narabayashi, H. Neurophysiological ideas on pallidotomy and ventrolateral thalamotomy for hyperkinesis. *Stereotactic and Functional Neurosurgery* **22**, 291–303 (1962).
161. Van Buren, J. M., Li, C.-L., Shapiro, D. Y., Henderson, W. G. & Sadowsky, D. A. A Qualitative and Quantitative Evaluation of Parkinsonians Three to Six Years Following Thalamotomy (Part 1 of 2). *Stereotactic and Functional Neurosurgery* **35**, 202–217 (1973).
162. Ohye, C. Depth microelectrode studies. *Stereotaxy of the human brain* 372–389 (1982).
163. Laitinen, L. Thalamic targets in the stereotaxic treatment of Parkinson's disease. *Journal of neurosurgery* **24**, 82–85 (1966).
164. Schwab, R. S. Neurological assessment of the deficits in Parkinson's disease before and after stereotactic surgery. *Stereotactic and Functional Neurosurgery* **27**, 218–224 (1966).
165. Siegfried, J. & Hood, T. Current status of functional neurosurgery. in *Advances and technical standards in neurosurgery* 19–79 (Springer, 1983).
166. Talairach, J., Hecaen, H., David, M., Monnier, M. & Deajuriaguerra, J. Recherches sur la coagulation thérapeutique des structures sous-corticales chez lhomme. *Revue neurologique* **81**, 4–24 (1949).
167. Selby, G. Stereotactic surgery for the relief of Parkinson's disease. 2. An analysis of the results in a series of 303 patients (413 operations). *J. Neurol. Sci.* **5**, 343–375 (1967).
168. Broager, B. The Surgical Treatment of Parkinsonism. *Acta Neurologica Scandinavica* **39**, 181–187 (1963).
169. Spiegel, E. A. *et al.* Campotomy. *Trans Am Neurol Assoc* **87**, 240–242 (1962).
170. Forel, A. Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehirne des Menschen und einiger Säugethiere, mit Beiträgen zu den Methoden der Gehirnuntersuchung. *Archiv für Psychiatrie und Nervenkrankheiten* **7**, 393–495 (1877).
171. Story, J. L., French, L. A., Chou, S. N. & Meier, M. J. Experiences with subthalamic lesions in patients with movement disorders. *Stereotactic and Functional Neurosurgery* **26**, 218–221 (1965).
172. Velasco, F. C., Molina-Negro, P., Bertrand, C. & Hardy, J. Further definition of the subthalamic target for arrest of tremor. *Journal of neurosurgery* **36**, 184–191 (1972).
173. Bertrand, C. Localization of lesions. in *Journal of Neurosurgery* vol. 24 446 (Amer Assoc Neurological Surgeons, Univ Virginia, 1966).
174. Hullay, J., Velok, J., Gombi, R. & Boczàn, G. Subthalamotomy in Parkinson's disease. *Stereotactic and Functional Neurosurgery* **32**, 345–348 (1970).
175. Fager, C. A. Evaluation of thalamic and subthalamic surgical lesions in the alleviation of Parkinson's disease. *Journal of neurosurgery* **28**, 145–149 (1968).
176. Gros, C., Frerebeau, P., Perez-Dominguez, E., Bazin, M. & Privat, J. M. Long term results of stereotaxic surgery for infantile dystonia and dyskinesia. *Neurochirurgia (Stuttg)* **19**, 171–178 (1976).
177. Markham, C. H., Brown, W. J. & Rand, R. W. Stereotaxic Lesions in Parkinson's Disease: Clinicopathological Correlations. *Arch Neurol* **15**, 480–497 (1966).

178. Rand, R. W., Crandall, P. H., Adey, W. R., Walter, R. D. & Markham, C. H. Electrophysiologic investigations in Parkinson's disease and other dyskinesias in man. *Neurology* **12**, 754–770 (1962).
179. Markham, C. H. & Rand, R. W. Stereotactic Surgery in Parkinson's Disease. *Archives of Neurology* **8**, 621–631 (1963).
180. Adams, J. E. & Rutkin, B. B. Lesions of the centrum medianum in the treatment of movement disorders. *Stereotactic and Functional Neurosurgery* **26**, 231–236 (1965).
181. Spiegel, E. A. Indications for stereoencephalotomies. A critical assessment. *Confin Neurol* **31**, 5–10 (1969).
182. Waltz, J. M., Riklan, M., Stellar, S. & Cooper, I. S. Cryothalamectomy for Parkinson's disease: A statistical analysis. *Neurology* **16**, 994–994 (1966).
183. Kalyanaraman, S. & Ramamurthi, B. Simultaneous bilateral stereotaxic lesions in the diencephalon. *Confin Neurol* **26**, 310–314 (1965).
184. Riechert, T. *Stereotactic Brain Operations: Methods, Clinical Aspects, Indications*. (Huber, 1980).
185. Shichijo, F. *et al.* A 10-Year Follow-up-Study of Bilateral VL Thalamotomy for Parkinson's disease. in *Applied Neurophysiology* vol. 46 317–317 (Karger Allschwilerstrasse 10, Ch-4009 Basel, Switzerland, 1983).
186. Laitinen, L. V., Bergenheim, A. T. & Hariz, M. I. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* **76**, 53–61 (1992).
187. Jeanmonod, D., Magnin, M. & Morel, A. Low–threshold calcium spike bursts in the human thalamus: Common physiopathology for sensory, motor and limbic positive symptoms. *Brain* **119**, 363–375 (1996).
188. Svennilson, E., Torvik, A., Lowe, R. & Leksell, L. Treatment of parkinsonism by stereotactic thermolesions in the pallidal region. A clinical evaluation of 81 cases. *Acta Psychiatr Scand.* **35**, 358–377 (1960).
189. Hariz, M. & Blomstedt, P. Leksell's Posteroventral Pallidotomy 1992–2022: Quo Vadis? *Stereotactic and Functional Neurosurgery* 1–5 (2022).
190. DeLong, M. R. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13**, 281–285 (1990).
191. Kuo, J.-S. & Carpenter, M. B. Organization of pallidothalamic projections in the rhesus monkey. *Journal of comparative Neurology* **151**, 201–235 (1973).
192. Carpenter, M. B., Nakano, K. & Kim, R. Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. *Journal of Comparative Neurology* **165**, 401–415 (1976).
193. Gross, R. E. *et al.* Relationship of lesion location to clinical outcome following microelectrode-guided pallidotomy for Parkinson's disease. *Brain* **122**, 405–416 (1999).
194. Iacono, R. P. *et al.* The results, indications, and physiology of posteroventral pallidotomy for patients with Parkinson's disease. *Neurosurgery* **36**, 1118–25 (1995).
195. Iacono, R. P. *et al.* Contemporaneous bilateral pallidotomy. *Neurosurgical Focus* **2**, E7 (1997).
196. Iacono, R. P. *et al.* Simultaneous bilateral pallidoansotomy for idiopathic dystonia musculorum deformans. *Pediatric Neurology* **14**, 145–148 (1996).
197. Sutton, J. P. *et al.* Ventroposterior medial pallidotomy in patients with advanced Parkinson's disease. *Neurosurgery* **36**, 1134–1141 (1995).
198. Schuurman, P. R., Bie, R. M. A. de, Speelman, J. D. & Bosch, D. A. Bilateral posteroventral pallidotomy in advanced parkinson's disease in three patients. *Movement Disorders* **12**, 752–755 (1997).
199. De Bie RM, Schuurman PR, Esselink RA, Bosch DA & Speelman JD. Bilateral pallidotomy in Parkinson's disease: A retrospective study. *Mov Disord.* **17**, 533–538 (2002).
200. Scott, R. *et al.* Neuropsychological, neurological and functional outcome following pallidotomy for Parkinson's disease. A consecutive series of eight simultaneous bilateral and twelve unilateral procedures. *Brain: a journal of neurology* **121**, 659–675 (1998).

201. Ghika, J. *et al.* Bilateral simultaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects: Report of four cases and review of the literature. *J Neurosurg* **91**, 313–321 (1999).
202. Favre, J., Burchiel, K. J., Taha, J. M. & Hammerstad, J. Outcome of unilateral and bilateral pallidotomy for Parkinson's disease: patient assessment. *Neurosurgery* **46**, 344–355 (2000).
203. Counihan, T. J., Shinobu, L. A., Eskandar, E. N., Cosgrove, G. R. & Penney Jr, J. B. Outcomes following staged bilateral pallidotomy in advanced Parkinson's disease. *Neurology* **56**, 799–802 (2001).
204. Intemann, P. M. *et al.* Staged bilateral pallidotomy for treatment of Parkinson disease. *Journal of Neurosurgery* **94**, 437–444 (2001).
205. Sobstyl, M., Zabek, M., Koziara, H. & Kadziolka, B. Bilateral pallidotomy for the treatment of advanced Parkinson disease. *Neurol Neurochir Pol.* **37**, 251–262 (2003).
206. Parkin, S. G. *et al.* Unilateral and bilateral pallidotomy for idiopathic Parkinson's disease: a case series of 115 patients. *Mov Disord.* **17**, 682–692 (2002).
207. Baron, M. S. *et al.* Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. *Ann Neurol* **40**, 355–366 (1996).
208. Dogali, M. *et al.* Stereotactic ventral pallidotomy for Parkinson's disease. *Neurology* **45**, 753–761 (1995).
209. Fazzini, E., Dogali, M., Sterio, D., Eidelberg, D. & Berić, A. Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. *Neurology* **48**, 1273–1277 (1997).
210. Lang, A. E. *et al.* Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med* **337**, 1036–1042 (1997).
211. Schrag, A. *et al.* Unilateral pallidotomy for Parkinson's disease: results after more than 1 year. *J Neurol Neurosurg Psychiatry* **67**, 511–517 (1999).
212. Samuel, M. *et al.* A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. *Brain* **121 (Pt 1)**, 59–75 (1998).
213. Samii, A. *et al.* Reassessment of unilateral pallidotomy in Parkinson's disease. A 2-year follow-up study. *Brain* **122 (Pt 3)**, 417–425 (1999).
214. Kim, R. *et al.* Efficacy of bilateral pallidotomy. *Neurosurgical Focus* **2**, E10 (1997).
215. Vitek, J. L. *et al.* Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. *Ann Neurol* **53**, 558–569 (2003).
216. Hariz, M. I. & Bergenheim, A. T. A 10-year follow-up review of patients who underwent Leksell's posteroventral pallidotomy for Parkinson disease. *J Neurosurg* **94**, 552–558 (2001).
217. Young, R. F. *et al.* Gamma knife radiosurgery as a lesioning technique in movement disorder surgery. *J Neurosurg* **89**, 183–193 (1998).
218. Lindquist, C., Kihlström, L. & Hellstrand, E. Functional neurosurgery-a future for the Gamma Knife? *Stereotactic and functional neurosurgery* **57**, 72–81 (1991).
219. Friehs, G. M. *et al.* Stereotactic radiosurgery for functional disorders. *Neurosurgical Focus* **23**, E2 (2007).
220. Ohye, C. & Shibazaki, T. Treatment of Functional Disorders with Gamma Knife Thalamotomy. *Japanese Experience with Gamma Knife Radiosurgery* **22**, 170–181 (2009).
221. Rand, R. W. *et al.* Gamma knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results. *Stereotactic and Functional Neurosurgery* **61**, 65–92 (1993).
222. Drummond, P. S., Pourfar, M. H., Hill, T. C., Mogilner, A. Y. & Kondziolka, D. S. Subthalamic Gamma Knife Radiosurgery in Parkinson's Disease: A Cautionary Tale. *Stereotact Funct Neurosurg* **98**, 110–117 (2020).
223. Campbell, A. M., Glover, J., Chiang, V. L., Gerrard, J. & James, B. Y. Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: a systematic review of the literature. *Radiotherapy and Oncology* **114**, 296–301 (2015).

224. Ohye, C., Shibazaki, T. & Sato, S. Gamma knife thalamotomy for movement disorders: evaluation of the thalamic lesion and clinical results. *Journal of Neurosurgery* **102**, 234–240 (2005).
225. Benabid, A. L. *et al.* Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *The Lancet* **337**, 403–406 (1991).
226. Schuepbach, W. M. M. *et al.* Neurostimulation for Parkinson's disease with early motor complications. *New England Journal of Medicine* **368**, 610–622 (2013).
227. Krack, P. *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine* **349**, 1925–1934 (2003).
228. Deuschl, G. *et al.* A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine* **355**, 896–908 (2006).
229. Young, R. F., Vermeulen, S., Posewitz, A. & Shumway-Cook, A. Pallidotomy with the gamma knife: a positive experience. *Stereotact Funct Neurosurg* **70 Suppl 1**, 218–228 (1998).
230. InSightec. *Evaluation of the Safety and Effectiveness of Bilateral Exablate Ablation of the Pallidothalamic Tract (PTT) for the Treatment of the Motor Complications of Parkinson's Disease (PD)*. https://clinicaltrials.gov/ct2/show/NCT04728295 (2021).
231. Alvarez, L. *et al.* Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. *Journal of Neurology, Neurosurgery & Psychiatry* **80**, 979–985 (2009).
232. Alvarez, L. *et al.* Dorsal subthalamotomy for Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society* **16**, 72–78 (2001).
233. Alvarez, L. *et al.* Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. *Brain* **128**, 570–583 (2005).
234. InSightec. *A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Globus Pallidum Using the ExAblate Neuro System*. https://clinicaltrials.gov/ct2/show/NCT03319485 (2020).
235. Nauta, W. J. & Mehler, W. R. Projections of the lentiform nucleus in the monkey. *Brain Res.* **1**, 3–42 (1966).
236. Sakai, S. T. & Smith, A. Distribution of nigrothalamic projections in the dog. *J Comp Neurol* **318**, 83–92 (1992).
237. Horisawa, S. *et al.* Unilateral pallidothalamic tractotomy for akinetic-rigid Parkinson's disease: a prospective open-label study. *Journal of Neurosurgery* **1**, 1–7 (2021).
238. Horisawa, S., Nanke, M., Kawamata, T. & Taira, T. Pallidothalamic Tractotomy for Parkinson Disease with 1-Year Follow-Up: A Case Report. *World Neurosurg* **121**, 193–195 (2019).
239. Horisawa, S. *et al.* Pallidothalamic Tractotomy (Forel's Field H1-tomy) for Dystonia: Preliminary Results. *World neurosurgery* **129**, e851–e856 (2019).
240. Godinho, F. *et al.* Stereotactic Lesion in the Forel's Field H: A Two-Years Prospective Open-Label Study on Motor and Nonmotor Symptoms, Neuropsychological Functions and Quality of Life in Parkinson Disease. *Neurosurgery* (2019) doi:10.1093/neuros/nyz039.
241. Rajput, A. H., Voll, A., Rajput, M. L., Robinson, C. A. & Rajput, A. Course in Parkinson disease subtypes a 39-year clinicopathologic study. *Neurology* **73**, 206–212 (2009).
242. Wächter, T., Mínguez-Castellanos, A., Valldeoriola, F., Herzog, J. & Stoevelaar, H. A tool to improve pre-selection for deep brain stimulation in patients with Parkinson's disease. *J Neurol* **258**, 641–646 (2011).
243. York, M. K. *et al.* Short and long-term motor and cognitive outcome of staged bilateral pallidotomy: a retrospective analysis. *Acta Neurochirurgica* **149**, 857–866 (2007).
244. Turner, K. R., Reid, W. G., Homewood, J. & Cook, R. J. Neuropsychological sequelae of bilateral posteroventral pallidotomy. *J Neurol Neurosurg Psychiatry* **73**, 444–446 (2002).

245. Sarica, C. *et al.* Trends and disparities in deep brain stimulation utilization in the United States: a Nationwide Inpatient Sample analysis from 1993 to 2017. *Lancet Reg Health Am* **26**, 100599 (2023).
246. Elias, W. J. *et al.* A pilot study of focused ultrasound thalamotomy for essential tremor. *N. Engl. J. Med.* **369**, 640–648 (2013).
247. DGN One | Leitlinie Details. https://dgn.org/leitlinie/tremor.
248. Martínez-Fernández, R. *et al.* Bilateral staged magnetic resonance-guided focused ultrasound thalamotomy for the treatment of essential tremor: a case series study. *J Neurol Neurosurg Psychiatry* **92**, 927–931 (2021).
249. Martínez-Fernández, R. *et al.* Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *The Lancet Neurology* **17**, 54–63 (2018).
250. Krishna Vibhor *et al.* Trial of Globus Pallidus Focused Ultrasound Ablation in Parkinson's Disease. *New England Journal of Medicine* **388**, 683–693 (2023).
251. Lin, F. *et al.* Comparison of efficacy of deep brain stimulation and focused ultrasound in parkinsonian tremor: a systematic review and network meta-analysis. *J Neurol Neurosurg Psychiatry* jnnp-2020-323656 (2021) doi:10.1136/jnnp-2020-323656.
252. Martínez-Fernández, R. *et al.* Staged Bilateral MRI-Guided Focused Ultrasound Subthalamotomy for Parkinson Disease. *JAMA Neurol* **81**, 638–644 (2024).
253. Mahajan, U. V. *et al.* Bilateral Deep Brain Stimulation is the Procedure to Beat for Advanced Parkinson Disease: A Meta-Analytic, Cost-Effective Threshold Analysis for Focused Ultrasound. *Neurosurgery* **88**, 487–496 (2021).
254. Shanker, V. Essential tremor: diagnosis and management. *BMJ* **366**, l4485 (2019).
255. Elble, R. J. What is Essential Tremor? *Curr Neurol Neurosci Rep* **13**, 353 (2013).
256. Louis, E. D. *et al.* Historical underpinnings of the term essential tremor in the late 19th century. *Neurology* **71**, 856–859 (2008).
257. Critchley, M. Observations on essential (heredofamilial) tremor. *Brain* **72**, 113–139 (1949).
258. Louis, E. D. & Ottman, R. Study of possible factors associated with age of onset in essential tremor. *Movement disorders: official journal of the Movement Disorder Society* **21**, 1980–1986 (2006).
259. Louis, E. D. The primary type of tremor in essential tremor is kinetic rather than postural: cross-sectional observation of tremor phenomenology in 369 cases. *European journal of neurology* **20**, 725–727 (2013).
260. Louis, E. D., Hernandez, N. & Michalec, M. Prevalence and correlates of rest tremor in essential tremor: cross-sectional survey of 831 patients across four distinct cohorts. *Eur. J. Neurol.* **22**, 927–932 (2015).
261. Louis, E. D., Borden, S. & Moskowitz, C. B. Essential tremor centralized brain repository: diagnostic validity and clinical characteristics of a highly selected group of essential tremor cases. *Movement disorders: official journal of the Movement Disorder Society* **20**, 1361–1365 (2005).
262. Poston, K. L., Rios, E. & Louis, E. D. Action tremor of the legs in essential tremor: prevalence, clinical correlates, and comparison with age-matched controls. *Parkinsonism & related disorders* **15**, 602–605 (2009).
263. Kestenbaum, M., Michalec, M., Yu, Q., Pullman, S. L. & Louis, E. D. Intention Tremor of the Legs in Essential Tremor: Prevalence and Clinical Correlates. *Movement Disorders Clinical Practice* **2**, 24–28 (2015).
264. Rajalingam, R. *et al.* The clinical significance of lower limb tremors. *Parkinsonism & Related Disorders* **65**, 165–171 (2019).
265. Louis, E. D. When Do Essential Tremor Patients Develop Head Tremor Influences of Age and Duration and Evidence of a Biological Clock. *Neuroepidemiology* **41**, 110–115 (2013).
266. Eken, H. N. & Louis, E. D. Agnosia for head tremor in essential tremor: prevalence and clinical correlates. *Journal of Clinical Movement Disorders* **3**, 4 (2016).

267. Koller, W. C., Busenbark, K., Miner, K. & Group, E. T. S. The relationship of essential tremor to other movement disorders: report on 678 patients. *Annals of neurology* **35**, 717–723 (1994).
268. Hopfner, F. *et al.* Testing for alcohol sensitivity of tremor amplitude in a large cohort with essential tremor. *Parkinsonism & Related Disorders* **21**, 848–851 (2015).
269. Bain, P. G. *et al.* A study of hereditary essential tremor. *Brain* **117**, 805–824 (1994).
270. Mostile, G. & Jankovic, J. Alcohol in essential tremor and other movement disorders. *Movement Disorders* **25**, 2274–2284 (2010).
271. Rajput, A. H., Jamieson, H., Hirsh, S. & Quraishi, A. Relative efficacy of alcohol and propranolol in action tremor. *Canadian Journal of Neurological Sciences* **2**, 31–35 (1975).
272. Campbell, J. M. *et al.* Balance and cognitive impairments are prevalent and correlated with age in presurgical patients with essential tremor. *Clinical Parkinsonism & Related Disorders* **6**, 100134 (2022).
273. Arkadir, D. & Louis, E. D. The balance and gait disorder of essential tremor: what does this mean for patients? *Therapeutic advances in neurological disorders* **6**, 229–236 (2013).
274. Cinar, N., Sahin, S., Okluoglu Onay, T. & Karsidag, S. Balance in essential tremor during tandem gait: is the first mis-step an important finding? *J Clin Neurosci* **20**, 1433–1437 (2013).
275. Prasad, S. *et al.* Shaky and unsteady: Dynamic posturography in essential tremor. *J Neurol Sci* **385**, 12–16 (2018).
276. Ondo, W. G., Sutton, L., Dat Vuong, K., Lai, D. & Jankovic, J. Hearing impairment in essential tremor. *Neurology* **61**, 1093–1097 (2003).
277. Benito-León, J., Louis, E. D., Bermejo-Pareja, F., & Neurological Disorders in Central Spain (NEDICES) Study Group. Reported hearing impairment in essential tremor: a population-based case-control study. *Neuroepidemiology* **29**, 213–217 (2007).
278. Louis, E. D. *et al.* Essential tremor-plus: a controversial new concept. *Lancet Neurol* **19**, 266–270 (2020).
279. Testa, C. M. Key issues in essential tremor genetics research: Where are we now and how can we move forward? *Tremor and other hyperkinetic movements* **3**, (2013).
280. Clark, L. N. & Louis, E. D. Challenges in essential tremor genetics. *Revue Neurologique* **171**, 466–474 (2015).
281. Hopfner, F. *et al.* Knowledge gaps and research recommendations for essential tremor. *Parkinsonism & Related Disorders* **33**, 27–35 (2016).
282. Tan, E. K. & Schapira, A. H. Hunting for genes in essential tremor. *European Journal of Neurology* **15**, 889–890 (2008).
283. Choe, M. *et al.* Purkinje cell loss in essential tremor: random sampling quantification and nearest neighbor analysis. *Movement Disorders* **31**, 393–401 (2016).
284. Louis, E. D. & Faust, P. L. Essential tremor pathology: neurodegeneration and reorganization of neuronal connections. *Nature Reviews Neurology* **16**, 69–83 (2020).
285. Louis, E. D. *et al.* Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* **130**, 3297–3307 (2007).
286. Gironell, A. The GABA Hypothesis in Essential Tremor: Lights and Shadows. *Tremor Other Hyperkinet Mov (N Y)* **4**, 254 (2014).
287. Rajput, A. H., Robinson, C. A., Rajput, M. L., Robinson, S. L. & Rajput, A. Essential tremor is not dependent upon cerebellar Purkinje cell loss. *Parkinsonism & related disorders* **18**, 626–628 (2012).
288. Symanski, C. *et al.* Essential tremor is not associated with cerebellar Purkinje cell loss. *Movement Disorders* **29**, 496–500 (2014).
289. Bertrand, C., Hardy, J., Molina-Negro, P. & Martinez, S. N. Tremor of attitude. *Stereotactic and Functional Neurosurgery* **31**, 37–41 (1969).
290. Ito, Z. Stimulation and destruction of the prelemniscal radiation or its adjacent area in various extrapyramidal disorders. *Confin Neurol* **37**, 41–48 (1975).

291. Obrador, S. & Dierssen, G. Observations on the Treatment of Intentional and Postural Tremor by Subcortical Stereotaxic Lesions. *SFN* **26**, 250–253 (1965).
292. Krayenbühl, H. & Yasargil, M. G. Relief of intention tremor due to multiple sclerosis by stereotaxic thalamotomy. *Stereotactic and Functional Neurosurgery* **22**, 368–374 (1962).
293. Mohadjer, M., Goerke, H., Milios, E., Etou, A. & Mundinger, F. Long-term results of stereotaxy in the treatment of essential tremor. *Stereotactic and functional neurosurgery* **54**, 125–129 (1990).
294. Cooper, I. S. & Lorenc, M. *Involuntary Movement Disorders*. (Hoeber Medical Division, Harper & Row, 1969).
295. Riechert, T. Operative Behandlung des Tremors der Multiplen Sklerose und des essentiellen Tremors. (1972).
296. Akbostanci, M. C., Slavin, K. V. & Burchiel, K. J. Stereotactic ventral intermedial thalamotomy for the treatment of essential tremor: results of a series of 37 patients. *Stereotactic and functional neurosurgery* **72**, 174–177 (1999).
297. Cooper, I. S. A cerebellar mechanism in resting tremor. *Neurology* **16**, 1003–1003 (1966).
298. Goldman, M. S., Ahlskog, J. E. & Kelly, P. J. The symptomatic and functional outcome of stereotactic thalamotomy for medically intractable essential tremor. *Journal of neurosurgery* **76**, 924–928 (1992).
299. Jankovic, J., Cardoso, F., Grossman, R. G. & Hamilton, W. J. Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. *Neurosurgery* **37**, 680–687 (1995).
300. Zirh, A., Reich, S. G., Dougherty, P. M. & Lenz, F. A. Stereotactic thalamotomy in the treatment of essential tremor of the upper extremity: reassessment including a blinded measure of outcome. *Journal of Neurology, Neurosurgery & Psychiatry* **66**, 772–775 (1999).
301. Park, Y.-S., Jung, N. Y., Na, Y. C. & Chang, J. W. Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Movement Disorders* **34**, 727–734 (2019).
302. Meng, Y. *et al.* Magnetic resonance-guided focused ultrasound thalamotomy for treatment of essential tremor: A 2-year outcome study. *Mov Disord* **33**, 1647–1650 (2018).
303. Ito, H., Yamamoto, K., Fukutake, S., Odo, T. & Kamei, T. Two-year Follow-up Results of Magnetic Resonance Imaging-guided Focused Ultrasound Unilateral Thalamotomy for Medication-refractory Essential Tremor. *Intern Med* **59**, 2481–2483 (2020).
304. Pahwa, R. *et al.* Long-term evaluation of deep brain stimulation of the thalamus. *Journal of neurosurgery* **104**, 506–512 (2006).
305. Lak, A., Segar, D., Mcdannold, N., White, P. & Cosgrove, R. Magnetic Resonance Image Guided Focused Ultrasound Thalamotomy. A Single Center Experience With 160 Procedures. *Frontiers in Neurology* **13**, (2022).
306. Chang, J. W. *et al.* A prospective trial of magnetic resonance–guided focused ultrasound thalamotomy for essential tremor: Results at the 2-year follow-up. *Ann Neurol.* **83**, 107–114 (2018).
307. Reil, J.C. Die sylvische Grube. *Arch. Physiol. (Halle)* **9**, 195–208 (1809).
308. Mesulam, M.-M. *Principles of Behavioral and Cognitive Neurology*. (Oxford University Press, 2000).
309. Mesulam, M. M. & Mufson, E. J. Insula of the old world monkey. I. Architectonics in the insulo-orbito-temporal component of the paralimbic brain. *J. Comp. Neurol.* **212**, 1–22 (1982).
310. Mesulam, M. M. & Mufson, E. J. Insula of the old world monkey. III: Efferent cortical output and comments on function. *J. Comp. Neurol.* **212**, 38–52 (1982).
311. Mufson, E. J. & Mesulam, M. M. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. *J. Comp. Neurol.* **212**, 23–37 (1982).
312. Roberts, T. S. & Akert, K. Insular and opercular cortex and its thalamic projection in Macaca mulatta. *Schweiz Arch Neurol Neurochir Psychiatr* **92**, 1–43 (1963).

313. Kaas, J. H. The evolution of brains from early mammals to humans. *Wiley Interdisciplinary Reviews: Cognitive Science* **4**, 33–45 (2013).
314. Semendeferi, K. & Damasio, H. The brain and its main anatomical subdivisions in living hominoids using magnetic resonance imaging. *Journal of Human Evolution* **38**, 317–332 (2000).
315. Augustine, J. R. The insular lobe in primates including humans. *Neurol. Res.* **7**, 2–10 (1985).
316. Craig, A. D., Chen, K., Bandy, D. & Reiman, E. M. Thermosensory activation of insular cortex. *Nat. Neurosci.* **3**, 184–190 (2000).
317. Peyron, R. *et al.* Role of operculoinsular cortices in human pain processing: converging evidence from PET, fMRI, dipole modeling, and intracerebral recordings of evoked potentials. *Neuroimage* **17**, 1336–1346 (2002).
318. Frot, M. & Mauguière, F. Dual representation of pain in the operculo-insular cortex in humans. *Brain* **126**, 438–450 (2003).
319. Brooks, J. C. W., Zambreanu, L., Godinez, A., Craig, A. D. B. & Tracey, I. Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* **27**, 201–209 (2005).
320. Mutschler, I. *et al.* Functional organization of the human anterior insular cortex. *Neurosci. Lett.* **457**, 66–70 (2009).
321. Small, D. M. Taste representation in the human insula. *Brain Struct Funct* **214**, 551–561 (2010).
322. Cauda, F. *et al.* Functional anatomy of cortical areas characterized by Von Economo neurons. *Brain Struct Funct* **218**, 1–20 (2013).
323. Stephani, C., Fernandez-Baca Vaca, G., Maciunas, R., Koubeissi, M. & Lüders, H. O. Functional neuroanatomy of the insular lobe. *Brain Struct Funct* **216**, 137–149 (2011).
324. Nieuwenhuys, R. The insular cortex: a review. *Prog. Brain Res.* **195**, 123–163 (2012).
325. Kurth, F., Zilles, K., Fox, P. T., Laird, A. R. & Eickhoff, S. B. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure and Function* **214**, 519–534 (2010).
326. Garcia-Larrea, L. The posterior insular-opercular region and the search of a primary cortex for pain. *Neurophysiol Clin* **42**, 299–313 (2012).
327. Evrard, H. C. The Organization of the Primate Insular Cortex. *Front Neuroanat* **13**, 43 (2019).
328. Craig, A. D. B. How do you feel--now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* **10**, 59–70 (2009).
329. Keysers, C., Kaas, J. H. & Gazzola, V. Somatosensation in social perception. *Nat Rev Neurosci* **11**, 417–428 (2010).
330. Jezzini, A., Caruana, F., Stoianov, I., Gallese, V. & Rizzolatti, G. Functional organization of the insula and inner perisylvian regions. *Proceedings of the National Academy of Sciences* **109**, 10077–10082 (2012).
331. Friedman, D. P. & Murray, E. A. Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *J. Comp. Neurol.* **252**, 348–373 (1986).
332. Ostrowsky, K. *et al.* Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb. Cortex* **12**, 376–385 (2002).
333. Frot, M., Magnin, M., Mauguière, F. & Garcia-Larrea, L. Human SII and posterior insula differently encode thermal laser stimuli. *Cereb. Cortex* **17**, 610–620 (2007).
334. Mazzola, L., Isnard, J., Peyron, R. & Mauguière, F. Stimulation of the human cortex and the experience of pain: Wilder Penfield's observations revisited. *Brain* **135**, 631–640 (2012).
335. Allman, J. M. *et al.* The von Economo neurons in frontoinsular and anterior cingulate cortex in great apes and humans. *Brain Struct Funct* **214**, 495–517 (2010).
336. Zaki, J., Davis, J. I. & Ochsner, K. N. Overlapping activity in anterior insula during interoception and emotional experience. *Neuroimage* **62**, 493–499 (2012).
337. Cauda, F. *et al.* Functional connectivity of the insula in the resting brain. *Neuroimage* **55**, 8–23 (2011).

338. Cerliani, L. *et al.* Probabilistic tractography recovers a rostrocaudal trajectory of connectivity variability in the human insular cortex. *Human brain mapping* **33**, 2005–2034 (2012).
339. Jakab, A., Molnár, P. P., Bogner, P., Béres, M. & Berényi, E. L. Connectivity-based parcellation reveals interhemispheric differences in the insula. *Brain Topogr* **25**, 264–271 (2012).
340. Mesulam, M. & Mufson, E. J. The insula of Reil in man and monkey. in *Association and auditory cortices* 179–226 (Springer, 1985).
341. Bonthius, D. J., Solodkin, A. & Van Hoesen, G. W. Pathology of the insular cortex in Alzheimer disease depends on cortical architecture. *Journal of Neuropathology & Experimental Neurology* **64**, 910–922 (2005).
342. Anderson, K. *et al.* The morphology of supragranular pyramidal neurons in the human insular cortex: a quantitative Golgi study. *Cerebral Cortex* **19**, 2131–2144 (2009).
343. Kurth, F. *et al.* Cytoarchitecture and probabilistic maps of the human posterior insular cortex. *Cerebral cortex* **20**, 1448–1461 (2010).
344. Öngür, D., Ferry, A. T. & Price, J. L. Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology* **460**, 425–449 (2003).
345. von Economo, C. F. & Koskinas, G. N. *Die Cytoarchitektonik Der Hirnrinde Des Erwachsenen Menschen*. (J. Springer, 1925).
346. Nimchinsky, E. A., Vogt, B. A., Morrison, J. H. & Hof, P. R. Spindle neurons of the human anterior cingulate cortex. *Journal of Comparative Neurology* **355**, 27–37 (1995).
347. Butti, C., Santos, M., Uppal, N. & Hof, P. R. Von Economo neurons: clinical and evolutionary perspectives. *Cortex* **49**, 312–326 (2013).
348. Seeley, W. W. Anterior insula degeneration in frontotemporal dementia. *Brain Structure and Function* **214**, 465–475 (2010).
349. Kim, E.-J. *et al.* Selective frontoinsular von Economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. *Cerebral cortex* **22**, 251–259 (2012).
350. Santos, M. *et al.* Von Economo neurons in autism: a stereologic study of the frontoinsular cortex in children. *Brain Res.* **1380**, 206–217 (2011).
351. Di Stefano, V. *et al.* Clinical presentation of strokes confined to the insula: a systematic review of literature. *Neurol Sci* **42**, 1697–1704 (2021).
352. Guillaume, M. M. J. Cinq cas de foyers épileptogènes insulaires opérés. *Soc Française de Neurol* 766–769 (1949).
353. Guillaume, M. M. J. Technique de resection de l'insula dans les epilepsies insulaires. *Rev Neurol* **81**, 900–903 (1949).
354. Penfield, W. & Jasper, H. Epilepsy and the functional anatomy of the human brain. (1954).
355. Ojemann, G. A. & Whitaker, H. A. Language localization and variability. *Brain and Language* **6**, 239–260 (1978).
356. Mazzola, L., Mauguière, F. & Isnard, J. Electrical Stimulations of the Human Insula: Their Contribution to the Ictal Semiology of Insular Seizures. *Journal of Clinical Neurophysiology* **34**, 307–314 (2017).
357. Guénot, M. Indications and risk of neurosurgical techniques in the adult presenting with drug-resistant partial epilepsy (radiosurgery included). *Revue Neurologique* **160**, 5S185-94 (2004).
358. Bourdillon, P. *et al.* Stereotactic electroencephalography is a safe procedure, including for insular implantations. *World neurosurgery* **99**, 353–361 (2017).
359. Ostrowsky, K. *et al.* Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. *Epilepsia* **41**, 681–686 (2000).
360. Isnard, J., Guénot, M., Ostrowsky, K., Sindou, M. & Mauguière, F. The role of the insular cortex in temporal lobe epilepsy. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **48**, 614–623 (2000).
361. Isnard, J., Guénot, M., Sindou, M. & Mauguière, F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. *Epilepsia* **45**, 1079–1090 (2004).

362. Pugnaghi, M. *et al.* Features of somatosensory manifestations induced by intracranial electrical stimulations of the human insula. *Clinical Neurophysiology* **122**, 2049–2058 (2011).
363. Afif, A., Minotti, L., Kahane, P. & Hoffmann, D. Anatomofunctional organization of the insular cortex: a study using intracerebral electrical stimulation in epileptic patients. *Epilepsia* **51**, 2305–2315 (2010).
364. Afif, A., Hoffmann, D., Minotti, L., Benabid, A. L. & Kahane, P. Middle short gyrus of the insula implicated in pain processing. *Pain* **138**, 546–555 (2008).
365. Mazzola, L. *et al.* Vestibular responses to direct stimulation of the human insular cortex. *Ann. Neurol.* **76**, 609–619 (2014).
366. Chouchou, F. *et al.* How the insula speaks to the heart: Cardiac responses to insular stimulation in humans. *Human Brain Mapping* **40**, 2611–2622 (2019).
367. Mazzola, L., Mauguière, F. & Isnard, J. Functional mapping of the human insula: Data from electrical stimulations. *Rev. Neurol. (Paris)* **175**, 150–156 (2019).
368. Nguyen, D. K. *et al.* Revisiting the role of the insula in refractory partial epilepsy. *Epilepsia* **50**, 510–520 (2009).
369. Rachidi, I. *et al.* The Insula: A Stimulating Island of the Brain. *Brain Sciences* **11**, 1533 (2021).
370. Morel, A., Gallay, M. N., Baechler, A., Wyss, M. & Gallay, D. S. The human insula: Architectonic organization and postmortem MRI registration. *Neuroscience* **236**, 117–135 (2013).
371. Gallay, D. S., Gallay, M. N., Jeanmonod, D., Rouiller, E. M. & Morel, A. The insula of Reil revisited: multiarchitectonic organization in macaque monkeys. *Cereb Cortex* **22**, 175–190 (2012).
372. Jones, E. G., Dell'Anna, M. E., Molinari, M., Rausell, E. & Hashikawa, T. Subdivisions of macaque monkey auditory cortex revealed by calcium-binding protein immunoreactivity. *J. Comp. Neurol.* **362**, 153–170 (1995).
373. Liu, J., Morel, A., Wannier, T. & Rouiller, E. M. Origins of callosal projections to the supplementary motor area (SMA): A direct comparison between pre-SMA and SMA-proper in macaque monkeys. *Journal of Comparative Neurology* **443**, 71–85 (2002).
374. Morel, A., Liu, J., Wannier, T., Jeanmonod, D. & Rouiller, E. M. Divergence and convergence of thalamocortical projections to premotor and supplementary motor cortex: a multiple tracing study in the macaque monkey. *European Journal of Neuroscience* **21**, 1007–1029 (2005).
375. Cappe, C., Morel, A., Barone, P. & Rouiller, E. M. The thalamocortical projection systems in primate: an anatomical support for multisensory and sensorimotor interplay. *Cerebral cortex* **19**, 2025–2037 (2009).
376. Cappe, C., Morel, A. & Rouiller, E. M. Thalamocortical and the dual pattern of corticothalamic projections of the posterior parietal cortex in macaque monkeys. *Neuroscience* **146**, 1371–1387 (2007).
377. Allman, J. M., Tetreault, N. A., Hakeem, A. Y. & Park, S. The von Economo neurons in apes and humans. *Am. J. Hum. Biol.* **23**, 5–21 (2011).
378. Allman, J. M., Watson, K. K., Tetreault, N. A. & Hakeem, A. Y. Intuition and autism: a possible role for Von Economo neurons. *Trends Cogn. Sci. (Regul. Ed.)* **9**, 367–373 (2005).
379. Simms, M. L., Kemper, T. L., Timbie, C. M., Bauman, M. L. & Blatt, G. J. The anterior cingulate cortex in autism: heterogeneity of qualitative and quantitative cytoarchitectonic features suggests possible subgroups. *Acta neuropathologica* **118**, 673–684 (2009).
380. Agid, Y. *et al.* Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? *Parkinson's disease and related disorders* 409–414 (2006).
381. Blomstedt, P., Sandvik, U. & Tisch, S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Movement Disorders* **25**, 1350–1356 (2010).
382. Fytagoridis, A., Sandvik, U., Aström, M., Bergenheim, T. & Blomstedt, P. Long term follow-up of deep brain stimulation of the caudal zona incerta for essential tremor. *J Neurol Neurosurg Psychiatry* **83**, 258–262 (2012).

383. Barbe, M. T. *et al.* DBS of the PSA and the VIM in essential tremor: A randomized, double-blind, crossover trial. *Neurology* **91**, e543–e550 (2018).
384. Sarnthein, J. & Jeanmonod, D. High thalamocortical theta coherence in patients with Parkinson's disease. *J. Neurosci.* **27**, 124–131 (2007).
385. Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V. & Jeanmonod, D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain* **129**, 55–64 (2005).
386. Sarnthein, J., Morel, A., Von Stein, A. & Jeanmonod, D. Thalamic theta field potentials and EEG: high thalamocortical coherence in patients with neurogenic pain, epilepsy and movement disorders. *Thalamus & Related Systems* **2**, 231–238 (2003).
387. Moazami-Goudarzi, M., Sarnthein, J., Michels, L., Moukhtieva, R. & Jeanmonod, D. Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients. *Neuroimage* **41**, 985–997 (2008).
388. Stern, J., Jeanmonod, D. & Sarnthein, J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage* **31**, 721–731 (2006).
389. Michels, L., Moazami-Goudarzi, M. & Jeanmonod, D. Correlations between EEG and clinical outcome in chronic neuropathic pain: surgical effects and treatment resistance. *Brain imaging and behavior* **5**, 329–348 (2011).
390. Jankovic, J., Tsui, J. & Bergeron, C. Prevalence of cervical dystonia and spasmodic torticollis in the United States general population. *Parkinsonism & Related Disorders* **13**, 411–416 (2007).
391. Müller, J. *et al.* The prevalence of primary dystonia in the general community. *Neurology* **59**, 941–943 (2002).
392. Defazio, G. The epidemiology of primary dystonia: current evidence and perspectives. *Eur J Neurol* **17 Suppl 1**, 9–14 (2010).
393. Wenning, G. K. *et al.* Prevalence of movement disorders in men and women aged 50–89 years (Bruneck Study cohort): a population-based study. *The Lancet Neurology* **4**, 815–820 (2005).
394. Albanese, A. *et al.* Phenomenology and classification of dystonia: a consensus update. *Movement disorders* **28**, 863–873 (2013).
395. Lehéricy, S., Tijssen, M. A. J., Vidailhet, M., Kaji, R. & Meunier, S. The anatomical basis of dystonia: Current view using neuroimaging. *Movement Disorders* **28**, 944–957 (2013).
396. Schrock, L. E., Ostrem, J. L., Turner, R. S., Shimamoto, S. A. & Starr, P. A. The subthalamic nucleus in primary dystonia: single-unit discharge characteristics. *Journal of neurophysiology* **102**, 3740–3752 (2009).
397. Starr, P. A. *et al.* Spontaneous Pallidal Neuronal Activity in Human Dystonia: Comparison With Parkinson's Disease and Normal Macaque. *Journal of Neurophysiology* **93**, 3165–3176 (2005).
398. Merello, M. *et al.* Neuronal globus pallidus activity in patients with generalised dystonia. *Movement disorders: official journal of the Movement Disorder Society* **19**, 548–554 (2004).
399. Nambu, A. *et al.* Reduced pallidal output causes dystonia. *Frontiers in Systems Neuroscience* **5**, 89 (2011).
400. Moll, C. K. *et al.* Asymmetric pallidal neuronal activity in patients with cervical dystonia. *Frontiers in systems neuroscience* **8**, 15 (2014).
401. Sanghera, M. K. *et al.* Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. *Neurosurgery* **52**, 1358–1373 (2003).
402. Sani, S., Ostrem, J. L., Shimamoto, S., Levesque, N. & Starr, P. A. Single unit "pauser" characteristics of the globus pallidus pars externa distinguish primary dystonia from secondary dystonia and Parkinson's disease. *Experimental neurology* **216**, 295–299 (2009).
403. Hutchison, W. D., Lang, A. E., Dostrovsky, J. O. & Lozano, A. M. Pallidal neuronal activity: implications for models of dystonia. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society* **53**, 480–488 (2003).
404. Vitek, J. L. *et al.* GPi pallidotomy for dystonia: clinical outcome and neuronal activity. *Adv Neurol* **78**, 211–219 (1998).

405. Cooper, I. S. Dystonia reversal by operation on basal ganglia. *Archives of neurology* **7**, 132–145 (1962).
406. Taira, T. & Hori, T. Stereotactic ventrooralis thalamotomy for task-specific focal hand dystonia (writer's cramp). *Stereotactic and functional neurosurgery* **80**, 88–91 (2003).
407. Morel, A., Magnin, M. & Jeanmonod, D. Efferent connections of the human striatum and pallidum: a nauta degeneration study. in *Basal Ganglia and Thalamus in Health and Movement Disorders* 61–65 (Springer, 2001).
408. Horisawa, S., Taira, T., Goto, S., Ochiai, T. & Nakajima, T. Long-term improvement of musician's dystonia after stereotactic ventro-oral thalamotomy. *Annals of Neurology* **74**, 648–654 (2013).
409. Horisawa, S. *et al.* Safety and long-term efficacy of ventro-oral thalamotomy for focal hand dystonia: A retrospective study of 171 patients. *Neurology* **92**, e371–e377 (2019).