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# AIMS Neuroscience

## Focus and Scope

AIMS Neuroscience is an international Open Access journal devoted to publishing peer-reviewed, high quality, original papers from all areas in the field of neuroscience. The primary focus is to provide a forum in which to expedite the speed with which theoretical neuroscience progresses toward generating testable hypotheses. In the presence of current and developing technology that offers unprecedented access to functions of the nervous system at all levels, the journal is designed to serve the role of providing the widest variety of the best theoretical views leading to suggested studies. Single blind peer review is provided for all articles and commentaries.

Topics are announced at least three months in advance of each issue with the submission date. Up to five articles, limited to 8000 words, will be published with as wide a range of theoretical views as possible on a given topic. Peer review of papers will be done in a month following the specified submission date. For those that are accepted, on-line publication of the uncorrected article occurs within seven days with the final corrected version done in six weeks. During the next month following acceptance, the authors of the articles will write a commentary paper of no more than 2000 words evaluating the other simultaneously published articles vis-à-vis their own, with the goals of synthesis, integration, and expansion where possible. For any obviously incompatible points, authors are asked to provide specific suggestions on ways to empirically address the points to clarify which is likely correct. These commentaries will be published in the next issue. At the time the original articles are published, a general call for additional commentary papers will occur, targeting submission within a month. These will be subjected to peer review and up to five new commentaries will be published the third month. The overall process is designed to foster productive interaction, leading to the generation of hybrid theories and new ideas.

Submission of theoretical papers that do not fall into planned topical areas and represent well-founded novel contributions are also encouraged. An open call for commentaries on the accepted articles will occur with the goal that these be received within a month followed by peer review within 4 weeks. The journal also encourages submission of empirical papers that relate to theory. The previously described rapid review and publication will occur with these articles.

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# Transitioning from PET/MR to trimodal neuroimaging: why not cover the temporal dimension with EEG?

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## **ABSTRACT**

*The possibility of multimodality imaging with PET/MR and the availability of field MRI has allowed to investigate novel aspects of neuropsychiatric conditions. One of the major barriers in current studies is the lack of an instrument that allows to accurately cover the temporal aspect under the same physiological conditions. The aim of this commentary is to provide our perspective on how the integration of EEG-PET-MR could be a solution to the current challenge in molecular imaging and seems to hold great promise in future pharmacological challenging-based studies, understanding different functional states of the brain, and could furthermore aid in the diagnostic and prognostic evaluations of neurocognitive disorders.*

**Keywords:** PET; MR; EEG; multimodality; neuroimaging

With the advent of ultra-high field imaging and integrated PET/MRI systems within the last decade, it seems that the field of neuropsychiatric research has unlocked the potential to reach new heights. This is because these ultra-high field MR-PET systems are known to yield superb spatial resolution along with highly specific molecular data [1]. However, in the study of neurocognitive disorders with fMRI, the lack of an accurate temporal aspect revealing instrument in the sub-second range had since recently been a barrier. This is where the possibility of a triple modality system comes into play.

Indeed, a study by Del Guerra et al. describe this type of EEG system appended to a 1.5T PET/MRI implemented with success within the framework of the EU project TRIMAGE and has been shown to allow comprehensive understanding of brain function (See Fig.1) [2]. This is because EEG electrode-mediated PET signal attenuation is negligible and PET electronics do not interfere with electrophysiological signals. Moreover, the EEG signal can reflect functional changes allowing investigation of brain dynamics since it can be modulated by pharmacological manipulations [3]. Furthermore, the integration of EEG makes it possible to overcome one of the major drawbacks of fMRI which uses the BOLD effect to indirectly measure brain function. This is because the delayed hemodynamic response decreases the temporal resolution of the BOLD effect [4]. This triple modality combination holds great promise in the investigation of pharmacological challenging-based emotional, social, and cognitive paradigms owing to the elimination of learning and order effects [3]. In addition, it also allows to investigate and define different functional states of the brain. Multimodality systems maximise patient comfort and are timesaving rendering them more compliant and reduce dropout during

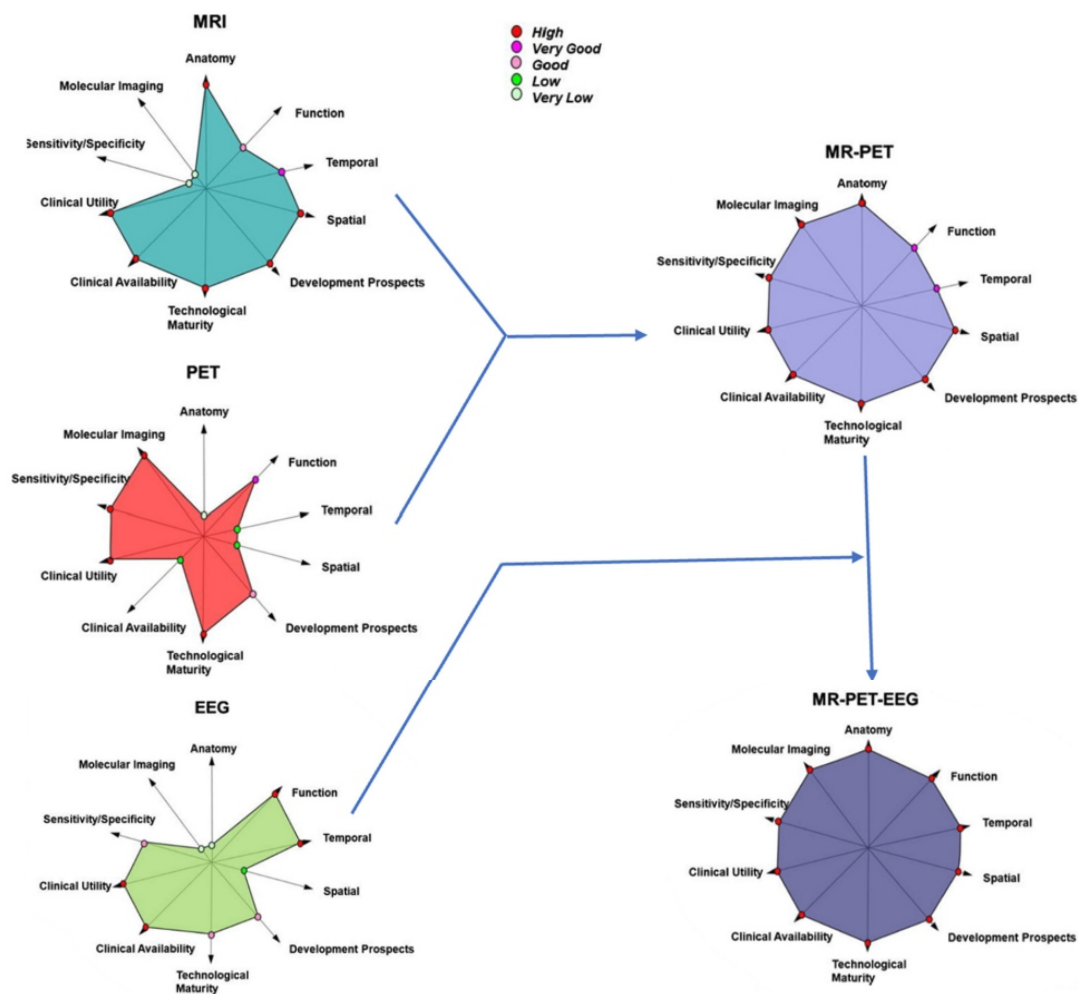
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What could be the possible clinical applications of such a trimodal system? For example, in a study by Golkowski et al. EEG/fMRI/PET was used to investigate brain activity in a small sample of patients with disorders of consciousness which they refer to as an approach that provides multiple markers of consciousness under the same physiological conditions, enabling a more accurate diagnosis and better estimation of prognosis which would be otherwise difficult to categorize [9]. The triple modality approach might also be valuable for investigating the fundamentals of brain function, for example, resting state networks that underpin many processes can be altered in disease states. A recent work by Régio Brambilla et al. showed that event related potential components that are affected by disease states and disorders can also be useful in this trimodal approach. In their study, task-induced changes in glutamatergic neurotransmission were found using the mismatched negativity paradigm which provides further evidence that EEG-fMRI-PET is a useful approach for investigating the role of glutamatergic neurotransmission in both the healthy and subjects suffering from disorders such as dementia and schizophrenia [10].

Nonetheless, implementation of such a system does not come without constraints. Great care is needed when recording data to maintain an acceptable level of data quality and to ensure patient safety during the procedure. There are also technical challenges due to artefacts, one of which is the “cardiobalistic artefact” occurring due to cardiac pulsatile activity causing pulsation of scalp vessels and head movements [5]. The other, caused by the switching of gradients during the preferred sequence for fMRI, the echo planar imaging sequence giving rise to the so-called “gradient artefact” [6]. Moreover, there are artefacts related to the currents induced due to the movement of conductive materials including the EEG electrodes and cables within the magnetic field also given that the scanner cryogen pump as well as gradient switching produces vibrations, and furthermore due to the inevitable motion of the study subject [7]. Even though there exist studies claiming that these artefacts may be removed with success through techniques such as Independent Component Analysis, Artefact Average Template Subtraction, etc. the real problem is that some of these artefacts have been shown to linearly increase with the increases in field strength and thus becoming more challenging to remove with their integration into ultra-high field scanners [8]. Lastly, there is the issue of integrating the different acquisition timeframes. Despite all the aforementioned technical and practical challenges in simultaneous PET/MR/EEG, richness of the complementary data obtained through numerous studies have elucidated that it is of potential added value in the diagnosis, treatment, and monitoring of neuropsychiatric disorders. Thus, we believe that with multimodal data integration through the use of machine learning methods and appropriate techniques to overcome these challenges encountered could in future reveal novel aspects of neuropsychiatric disorders [11].





**Figure 1.** Diagrams pertaining to each of MRI, PET, PET/MRI, PET/MRI/EEG, showing the strengths of the relevant attributes presented along each axis. The further the point is from the centre, the higher is the strength of the relevant attribute. Notice how the integration of EEG to the PET/MRI markedly strengthens temporal mapping of brain function.

### Conflicts of interest

The author has no conflicts of interest to declare.

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## Neuroimaging with SPECT-MRI: a myth or reality?

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Neuroimaging techniques are critical for the study of the human brain and the diagnosis and treatment of neurological disorders. Among these techniques, single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) are well-established methods for functional and structural imaging, respectively. The combination of these two techniques, known as SPECT-MR, has emerged as a promising modality for neuroimaging research and clinical practice [1]. SPECT-MR combines the strengths of SPECT and MRI to provide a comprehensive view of the brain's functional and structural properties. SPECT relies on the injection of a radiotracer, which emits gamma rays that are detected by a gamma camera. This produces a 3D image of the distribution of the radiotracer in the brain, reflecting local blood flow or metabolism. MRI, on the other hand, uses strong magnetic fields and radio waves to produce high-resolution images of the brain's anatomy. In SPECTMR, the SPECT data is co-registered and fused with the MRI data to create a single image that integrates functional and structural information. This is achieved by using specialized software that combines the SPECT and MRI data and allows for visualization of the functional changes in the context of the brain's structure. See Figure 1 [2]. A combined SPECT/MRI platform was first proposed in 2007 by Breton et al. who used a single pinhole SPECT system adjacent to a 0.1T magnet. The low MRI field strength made this solution suboptimal for use in routine preclinical research. However, since then systems combining SPECT and MRI have been introduced with both higher SPECT sensitivity and resolution and higher MRI field strengths [17]. To date, the SPECT/MRI system has been introduced to the market exclusively by MR Solutions (UK) allowing for sequential imaging of small animals at 9.4T, while simultaneous imaging systems are not yet commercially available [6]. One advantage of SPECT-MR is its ability to provide both functional and structural information of the brain in a single imaging session. This can reduce the need for multiple imaging sessions and increase patient comfort and convenience. Additionally, SPECT-MR has a higher spatial resolution than traditional SPECT imaging, which allows for more precise localization of functional changes within the brain [7]. SPECT is an attractive alternative to PET for preclinical studies due to its potential for better spatial resolution resulting from pinhole magnification. Additionally, SPECT allows for the use of multiple radionuclides that target different biomarkers and can use longer-lived and more accessible radionuclides. Operating costs for SPECT are also lower than for PET. Combining SPECT with MRI has further advantages, including providing high-contrast anatomical images that can be combined with SPECT acquisitions and using multiple pulse sequences to provide complementary functional measures, such as MR-spectroscopy. The availability of high-resolution anatomy from MRI, which has superior soft tissue contrast compared to CT (and lacks ionizing

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radiation), can also aid in SPECT quantification with correction for partial volume effects [15,16].

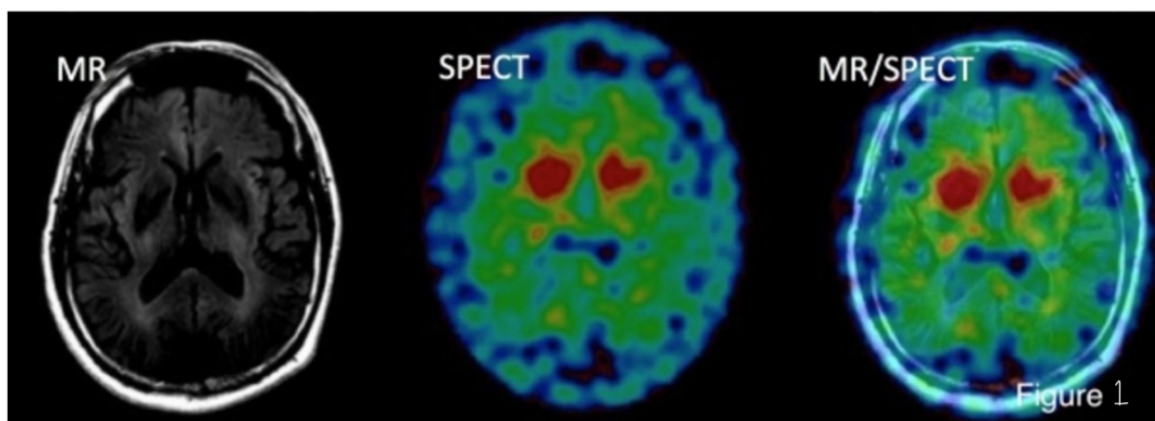
SPECT-MR has many potential applications in neuroscience research and clinical practice. One major application is in the diagnosis and management of neurological and psychiatric disorders. SPECT-MR can be used to identify patterns of brain activity associated with different disorders, such as Alzheimer's disease, epilepsy, and depression. This can lead to more accurate diagnoses and more effective treatment strategies [3,4]. SPECT-MR can be used to identify the epileptogenic focus in patients with epilepsy. The process of co-registering ictal SPECT with MRI, similar to PET, can enhance its precision and ability to exhibit more accurate anatomical localization. This innovative method is known as subtraction ictal SPECT co-registered with MRI (SISCOM) and has been linked to favorable postoperative outcomes and eradication of seizures when used to identify the epileptogenic focus. Moreover, SPECT co-registered with MRI is beneficial in pinpointing the precise location for the placement of intracranial EEG leads during invasive recording, thereby minimizing potential complications. It is also capable of detecting the ictal focus with high sensitivity in cases of extratemporal lobe epilepsy [5]. SPECT-MR can be used to study the regional cerebral blood flow in patients with Alzheimer's disease. By combining SPECT with MR, it is possible to identify the specific regions of the brain that show reduced blood flow and metabolism, allowing for targeted treatment [8]. SPECT-MR can be used to study the dopaminergic system in patients with Parkinson's disease. The SPECT component can provide functional information about the dopaminergic system, while the MR component can provide high-resolution anatomical details. Also, it has been shown that advanced MRI techniques as diffusion-weighted imaging, diffusion-tensor imaging, MR-spectroscopy, magnetization transfer imaging, and magnetic resonance imaging-based volumetry are more delicate in separating PD from atypical parkinsonian syndromes. By combining these two imaging modalities, clinicians can precisely locate the area of abnormal dopaminergic activity, which is critical in the diagnosis and management of Parkinson's disease [9,10]. SPECT-MR can be used to study the metabolism and blood flow in brain tumors. The SPECT component can provide functional information about the tumor's blood flow and metabolism including receptor binding, uptake and metabolism of exogenous compounds, hemodynamics, etc. while the MR component can provide high-resolution anatomical details. By combining these two imaging modalities, clinicians can accurately locate the tumor and assess its growth and response to treatment [11]. Another application of SPECT-MR is in the study of brain function and cognition. SPECT-MR can be used to map changes in brain activity associated with specific tasks, such as language processing, memory encoding, and emotion regulation. This can help researchers understand how the brain works and how different regions of the brain interact with each other [12]. SPECT-MR also has potential applications in the study of drug development and pharmacology. By mapping changes in brain activity associated with different drugs, SPECT-MR can help researchers identify new therapeutic targets and evaluate the efficacy of different treatments [13].

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However, there are also some limitations to SPECT-MR. SPECT-MR is a relatively new imaging technique, and as such, it is not widely available in all hospitals and medical centers. This is also related to the cost and complexity of the technique, which may make it less accessible to some researchers and clinicians. One limitation is its relatively low temporal resolution since SPECT is dependent on the haemodynamic response and sufficient detection of photon emissions, which limits its ability to capture rapid changes in brain activity. In addition, there are technical challenges: SPECT-MR requires specialized expertise and equipment. The complexity of the imaging process and the need for advanced data analysis can lead to technical challenges that require highly skilled personnel [14].

SPECT-MR is a promising imaging modality that has the potential to advance our understanding of the brain and its disorders. While there are still some technical and practical limitations to be overcome, ongoing research and development in this area hold great promise for the future of neuroscience research and clinical practice. The integration of functional and structural imaging with SPECT-MR represents a significant step forward in neuroimaging and has the potential to improve our understanding of brain function and lead to better diagnoses and treatments for neurological and psychiatric disorders [15].



**Figure 1.** MR and SPECT images have been fused to create a MR/SPECT image. Adapted from Takeshi Hara et al. (2016) *J Nucl Med.* 57:1936.

### Conflicts of interest

The author has no conflicts of interest to declare.

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# Adapting patient treatment of neurological diseases during the COVID19 pandemic

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## **ABSTRACT**

*Treating neurological patients during the pandemic period has become extremely challenging. At the same time, responding properly to these challenges has been diverse around the world, with varying levels of readiness, discipline, and approach. Additionally, there are significant differences in healthcare resources and processes between nations, and even within a nation, and these have significantly influenced the treatment procedure throughout the pandemic. However, neurologists have been called to care for patients with neurological symptoms who have COVID-19, and to continue managing COVID-19-affected neurological comorbidities in patients as before. This study highlights how the treatment procedures for neurological diseases are rapidly changing due to the spread of the SARS-CoV-2 virus. It also focuses on the challenges healthcare professionals are facing while providing proper treatment to neurological patients during the pandemic situation. Lastly, it offers some useful recommendations regarding the effective management of neurological diseases during the COVID-19 pandemic period.*

**Keywords:** *clinical neuroscience; neurologist; neurology; SARS-CoV-2*

## **1. Introduction**

Epidemics have caused social and demographic changes throughout history. The bubonic plague changed the course of the Middle Ages by slowing the rate of societal advancement in addition to killing a great number of people. In a short amount of time, the public's perception of the new coronavirus, SARS-CoV-2, has shifted. Although social isolation is a vital goal, its effects have caused people to make judgments that they would never have before. Healthcare systems have been compelled to adapt quickly to the new reality, adopting choices that are in the patient's best interests but also have unintended side effects. Because of the allocation of resources to this urgent issue that is seen as decisive, care for patients with other diseases has been reduced as a result of giving patients with SARS-CoV-2 infection priority [1].

Consequently, many patients may experience unfavorable effects from the distraction effect, hence attempts are made to avoid this. According to case reports and particular investigations of hospitalized patients, the prevalence of neurological symptoms among COVID-19 patients appears to be modest. However, there is a chance that the virus may enter the nervous system by circulation, an upper transcribrial, or a conjunctival channel [2]. As neurological diseases are the primary cause of disability worldwide, the epidemic could have adverse effects on other neurological patients if they do not receive specialized care [1].



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## 2. Influence of COVID-19 pandemic and confinement on neurological patients

Orsini et al. [2] highlighted that the neurological effects of SARS-CoV-2 are similar to those of other coronaviruses. The virus itself or the systemic effects of the infection may directly cause such involvement, which has been seen in more severe cases. COVID-19 could emerge with fewer usual symptoms (namely flu-like symptoms) in the elderly and in those with cardiac or endocrinological comorbidities, as opposed to more severe neurological manifestations. 78 out of 214 patients (36.4 percent) in the extensive investigation by Mao et al. [3] did exhibit neurological signs due to COVID-19. The most frequent of these symptoms were headache and dizziness, while peripheral nervous system (PNS) manifestations mostly involved changes in taste and smell (up to 5.6 and 5.1 percent of patients, respectively). Similarly, according to Nordvig et al. [4], potential neurological complications of COVID-19 include headache, fatigue, anosmia, dizziness, anorexia, ageusia, meningoencephalitis, myalgias, altered consciousness, hemorrhage, Guillain-Barré Syndrome, seizure, syncope, and stroke. Neuromuscular disease (NMD) patients are also thought to be more vulnerable to COVID-19 problems than the general population [2]. Some of them, such as individuals who have swallowing and breathing muscles involved, have other comorbid conditions, or are receiving IST (e.g., steroids), may be more susceptible to infection. In addition, infections, like those that cause spinal muscular atrophy or myasthenia gravis, can cause diseases like NMD to worsen or develop, and those who have both NMD and acute respiratory illnesses have a considerably higher risk of respiratory failure and a greater need for intensive care [2]. Avula et al. [5], Markus and Brainin [6], Paterson et al., [7] also found that SARS-CoV-2, like other viruses and bacteria, has been linked to a number of cases of acute cerebrovascular disorders (CVD), including ischemic or hemorrhagic stroke and cerebral venous sinus thrombosis. 505 adult patients with neurological symptoms were assessed at the Emergency Department (ED) between 20 February and 30 April 2020 by Pilotto et al. [8]. It was discovered that neurological patients with COVID-19 had a poor prognosis, as evidenced by greater hospitalization rates, a high mortality rate, and higher impairment after discharge. This emphasizes the negative effects of COVID-19 on neurological patients, who are more prone to early deterioration and death regardless of age or premorbid condition due to their fragility and vulnerability. Additionally, COVID-19 infection has been specifically shown by Pilotto et al. [8] to alter the clinical presentations and treatment of neurological patients. The organization of healthcare and daily practices are both significantly impacted by this. According to Matas-Guiu et al. [1], medical care delivery has been influenced by confinement, which was a component of the plan to stop the spread of COVID-19. This is especially important for neurological patients since they frequently have risk factors, like advanced age and disability, that raise the likelihood of a worse outcome in the event of infection. Additionally, these patients typically have a companion when they attend consultations; however, because of the pandemic, this has become extremely challenging, impacting the conventional forms of neurological treatment employed in

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consultations. Implementing telemedicine in patient care is difficult despite the availability of the necessary resources, even though it has become essential for healthcare team management and maintaining the delivery of neurological care while preventing the transmission of SARS-CoV-2 between patients, their relatives, nurses, neurologists, and researchers.

Without a doubt, the COVID-19 epidemic has changed how neurology is practiced and how patients with movement disorders are managed around the world. Many neurologists were forced to practice from their homes and devise new methods for managing neurological patients remotely as a result of the global lockdown. Some neurologists were forced to perform internal medicine when more staff was required. All of these improvements, though, have been incredibly difficult to implement, particularly given the need for them to be done safely, swiftly, and effectively [9]. For these reasons, clinicians are trying to make judicious decisions in deciding if the advantages of admission or intervention outweigh the use of resources and potential risks under the current crisis. The neurological intensive care units (ICUs) are often called upon for co-management, even though these beds and staff are also required for COVID-19 overflow. In addition, resources like thrombectomy are specifically reserved for patients that need the most. Neurologic patients with COVID-19 are also isolated from neurology patients without the disease [10]. Even in some cases, as in Italy, the majority of hospitals have reallocated neurologists for helping patients with COVID-19 [11].

### **3. New measures taken to treat patients with neurological diseases during pandemic**

As found by Matas-Guiu et al. [1], various steps are taken to treat neuro patients during the pandemic period, such as creating a functional reorganization plan, using telephone consultations to maintain neurological care, making decisions about periodic in-hospital treatments and complementary testing, providing care at a unit outside the hospital for emergency patients, and prioritizing patients with epilepsy using specific telephone services. Additionally, when a large number of people are infected with the virus, it is very difficult to organize neurological emergencies and admissions. So, all concerned need to be sincere and agile in treating emergency neurological patients to enhance the effectiveness of their treatment process.

According to Venketasubramanian et al. [12] protected channels are being turned on for all patients who have infections, whether they are suspected or proven. Even if protected pathways for stroke patients with suspected or confirmed COVID-19 are set up, a lack of qualified staff may make it difficult to evaluate and keep track of these patients' neurologic condition. In this circumstance, inpatient telemedicine has emerged as a key technique for enabling stroke team members to carry out crucial neurological monitoring of patients in designated COVID-19 areas, while minimizing person-to-person contact and preserving limited PPE supplies. Using telemedicine technology, evaluations of stroke patients are carried out fully digitally both in the emergency room and during routine hospital rounds.

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Additionally, a telestroke network enables patients with low ABCD2 scores to receive treatment in outlying hospitals rather than being needlessly sent to comprehensive stroke centers, particularly when the Emergency Rooms (ERs) are overburdened with COVID-19 management tasks.

In addition to getting standard-of-care imaging, all confirmed or suspected COVID-19 patients with acute stroke are also being assessed for intravenous thrombolysis and/or intra-arterial mechanical thrombectomy (MT). All patients are needed to wear surgical masks while being transported to imaging suites, but those who have suspected COVID-19 in particular must have supplemental oxygen applied underneath the mask using nasal prongs or other similar equipment. All medical staff members who come into direct physical contact with patients must also put on the proper PPE, such as a full sleeved gown, surgical mask, eye protection, and gloves. Additionally, the majority of medical facilities are continuing to use a uniform strategy for imaging patients who have suffered an ischemic stroke in the context of COVID-19. Facilities that previously relied on CT/CTA/CTP continue to do so, and centers that previously relied on MRI/MRA/MRP are doing the same. A COVID-19 imaging suite that can handle all patients with COVID-19 has started to be adopted by facilities with numerous CT or MRI scanners. To prevent the infection of healthy patients in CT scanners, this is the preferred way [12].

#### **4. The use of technology to treat neuro patients during pandemic**

It is important to analyze whether telemedicine can be used over extended periods of time to serve huge numbers of patients, as it has previously been suggested as a reaction in the event of a disaster [1]. Despite the existence of telestroke programs before the pandemic, the pandemic's situation necessitated adapting patients' access to neurological care to protect the staff caring for these patients. It was also necessary to make decisions regarding patients with stroke who also present SARS-CoV-2 infection. The usage of previously sporadic resources, including email and other electronic tools, has increased due to the need to respond to emergencies, monitor patients with chronic but changing diseases, and continue to provide therapy. The drawback of these technologies is that they are frequently not used by patients because of their advanced age or the features of their illnesses [13]. Neurologists may be able to evaluate clinical changes remotely with the help of images or videos that patients or their family members have captured; for instance, the video may be used to assess gait, balance, and oculomotor abnormalities. All of these techniques have made it possible for neurology departments to continue offering care and patient follow-up despite the situation [1].

Moro & Fernandez, [9] also contended that the clinical conditions of many patients with Parkinson's disease (PD), Huntington's disease, dystonia, or tics often deteriorate as they are unable to visit their neurologists regularly due to lockdown. To solve these problems, several actions have been taken, and telemedicine is deemed the most successful one among them. Particularly, when the treatment procedure is not time-sensitive, then telemedicine procedure is widely used due to its efficacy and ease. Moro &

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Fernandez, [9] described how an innovative two-tiered telemedicine model is implemented in Italy, where allied health professionals first conducted a telephone triage to determine the needs of their parkinsonian patients. This reduced the volume of patients who required more involved virtual visits with neurologists.

As argued by Chen & Hemmen [10], when treating high-risk groups, telemedicine platforms are essential. Pre-pandemic literature claimed that, for all neurology subspecialties, telemedicine was not less effective than in-person clinic visits. In response to the pandemic, Medicare coverage was extended outside rural regions, and tele-HIPAA regulations were relaxed. This sped up widespread adoption. The technology is adaptable and has been expanded to include neuro-rehabilitation, giving a hotline to prevent isolation among the elderly and disabled, and monitoring using remote equipment (such as accelerometers for Parkinson's disease). Telemedicine proponents emphasize the "4 Cs": improved patient comfort, convenience, better access to care, and confidentiality [10].

Markus and Brainin [6] also argued that telemedicine can be effectively used for acute assessment of thrombolysis. This is an essential component of stroke therapy, especially in remote areas, and expanded telemedicine use may be helpful during the current epidemic. With this approach, the stroke team's exposure to risk is decreased, a reasonable stroke evaluation is possible, unnecessary inter facility transfers are avoided, and the usage of mandatory personal protective equipment is avoided. Telemedicine is a good option for stroke outpatient follow-up as well as acute stroke. It permits followup while preserving the social isolation imposed in many nations. This can be done over the phone, but visual teleconferencing allows for better patient engagement and more limited examination. With outstanding patient experience comparable to in-person sessions, video teleconferencing has been proven to be well-suited for outpatient follow-up of patients with uncommon stroke disorders [6].

##### 5. Challenges posed by COVID-19 regarding neurological treatment and research

Worldwide, neurological disorders are the main factor in disability. However, any epidemic or pandemic, like the COVID-19 one, can have detrimental effects on people who have neurological conditions. Due to the epidemic's heavy toll, these patients struggle to receive the right care. The policy of confinement has affected the delivery of medical treatment since it aims to stop the spread of pandemic diseases. The neurological community should take note of this in particular. Many patients have risk factors such as advanced age, heart conditions, diabetes mellitus, and other disability-causing conditions. These elements raise the possibility of neurological illnesses having a bad prognosis. Additionally, these patients typically need to bring companions with them for consultations, and because of the epidemic, this has become extremely challenging, impacting the conventional forms of neurological care employed in consultations [13].

Current major clinical studies related to neurology have also faced numerous difficulties as a result of COVID-19. Enrollment has been halted due to quarantine and travel restrictions, and tight study

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guidelines put a lot of logistical pressure on research staff. However, there is still a moral requirement to finish these research studies out of respect for the current study participants. The study group handles this in a complicated and unique way. As the pandemic passes, it will be necessary to account for and further investigate both the direct (such as the loss of participants or data) and indirect (such as the infection as a confounder) effects of the pandemic.

## **6. Recommendations**

If neurologists identify that one of their patients is affected by the SARS-CoV-2 virus, then they need to be particularly careful about their treatment process, as the prognosis may be influenced by the underlying neurological condition. If new progression or symptoms of neurological disease emerge, neurologists should make the proper decision and analyze the risks and benefits of visiting the hospital, and it needs to be assessed individually. If remote follow-up can be possible and effective, then it should be prioritized by the neurologists. However, when in-hospital treatments are preferred, then there should not be any delays. In short, neurologists should analyze the case of the patients individually, consider the need for emergency in-hospital treatments, and take the appropriate action for the betterment of the patients [13]. In hospitals, a ‘secure’ off-site care unit should be created for treating patients with neurological emergencies or when continued administration of treatments becomes essential. This secure unit may also be useful when telephone consultation is not enough, like when multiple sclerosis relapses or myasthenia gravis symptoms exacerbate [1].

It is also crucial to consider the need for physical separation between the doctor and the patient during the pandemic period. Furthermore, patients should attend consultations alone whenever possible, lumbar punctures should only be performed when necessary, eye fundus examinations should be avoided whenever possible to reduce the amount of time that the doctor and patient are in close proximity, and the clinical examination should focus on the symptoms that motivated the consultation in order to keep the time spent in that proximity to a minimum. Despite these factors, certain individuals necessitate complicated therapies or crucial diagnostic procedures, requiring visits to the hospital. New, individualized forms of consultation are required in these circumstances. Prior to the consultation, patients' temperatures should be taken. Those who have a fever should be seen alone, and all safety precautions should be followed. The choice entails comparing the possibility of virus transmission against the potential advantages of the planned procedure or investigation. Patients must be followed up and given immediate access to the neurology department under certain conditions. For instance, epileptic episodes pose a problem for individuals who are isolated. In order to maximize therapy outside of the hospital, care must be improved in the case of an emergency or prospective emergency in addition to ongoing seizure monitoring and treatment. Typically, patients are provided with emergency action plans and rescue drugs, which may be administered by their families [1].

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Bhaskar et al. [14] advised that following procedures need to be followed for patients with neurological symptoms during the pandemic period:

- Patients should be watched for any short-term or long-term neurological or cognitive problems. Clinicians could evaluate cognitive impairment using standard measures like the Mini-Mental State Examination (MMSE). If the test has a good sensitivity/specificity balance (>85%), it can also be administered on a large scale by telephone, informant proxy, or directly by mail [such as the Cognitive Assessment Screening Test (CAST)].
- If a patient later develops neurological symptoms, it is important to determine whether they have ever had COVID-19 infection as well as the severity of their clinical condition and any supporting imaging results.
- Additionally, imaging could be utilized to evaluate the blood-brain barrier (BBB's) damage and determine whether COVID-19 causes a temporary or permanent change. Evaluation and permeability quantification of BBB could be carried out in one of two ways: (a) semi quantitatively by comparing scans taken before and after contrast injection; or (b) quantitatively by using perfusion-weighted or permeability magnetic resonance imaging (MRI) technique in comparison to dynamic contrast-enhanced MRI (DCE-MRI).

In order to treat patients with acute neurological conditions, Bhaskar et al. [14] also recommended using telemedicine whenever possible, maintaining social isolation of patients visiting hospitals and other facilities within clinics, and separating individuals with fever and respiratory symptoms from those without these symptoms as a way to lessen the impact. Proper training, including simulation training, should be offered to healthcare professionals regarding the treatment of neurological patients. These healthcare workers should also be given regular breaks so that they can avoid stress and fear.

They should also be provided with the required information related to relaxation and coping strategies. Online peer-support communities for discussion, together with social media and messaging chat groups, may offer a useful outlet for neurologists.

Venketasubramanian et al. [12] with the involvement of a large international panel of stroke experts, evaluated the rapidly expanding body of research on COVID-19 stroke, and offered recommendations for stroke management in this difficult new environment. The recommendations included changes for prehospital emergency rescue and hyperacute care, inpatient stroke or intensive units, post-hospitalization rehabilitation, follow-up with at-risk families and communities, and multispecialty departmental developments in the allied professions.

In the context of Coronavirus disease 2019 (COVID-19), it is also crucial to address acute neurological diseases, especially acute ischemic stroke, given the risk of infection for patients and healthcare professionals as well as mounting evidence of the virus's propensity to become neuroinvasive. The safety and well-being of the patients as well as the frontline healthcare staff must be taken into account

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while developing procedures for the management of continuing acute neurological care and intervention. In order to reduce viral exposure to healthcare personnel and patients, Bhaskar et al. [14] looked at existing pathways and their effectiveness. They then developed a holistic method to handle patients with acute neurological disorders in the COVID-19 scenario. For instance, as suggested by Bhaskar et al. [14], when treating individuals with acute ischemic stroke during COVID-19, a conservative approach comprising fever screening, history taking to rule out COVID-19 hazards, and the presence of infectious symptoms may become essential. To reduce the danger of infection, it has been recommended to limit the number of healthcare personnel in the patient's room, set rules for wearing personal protective equipment, and assign certain duties to different people.

Neurologists interact with the COVID-19 population in addition to stroke patients for symptoms including anosmia, headache, encephalopathy, or meningitis-encephalitis. To categorize a COVID-19 patient and avoid replacing a clinical evaluation with proxy diagnostics due to the danger of infection, specific measures must be done. Ancillary testing (such as CT scans and EEG) involves employees at risk for viral exposure in addition to the equipment that needs to be sanitized. However, if necessary, the standard of care shouldn't be withheld because of COVID-19. Given the variation in risk tolerance across people, a standardized methodology may aid in removing these potential biases in the diagnosis of COVID-19 patients. Finally, because mechanical ventilators and ICU resources are required, medical teams must be realistic but thorough when predicting the prognosis of catastrophic neurologic disease to help with resource allocation [10].

Orsini et al. [2] reported that COVID-19 is linked to neurological symptoms such as vertigo, headache, taste and smell disturbances, and issues affecting the nervous system that are ultimately brought on by the pathologic processes induced by SARS-CoV-2. Younger people appear to be less likely to develop severe types of COVID-19. However, neurological symptoms have also been found in pediatric patients, and the infection sometimes had long-term neurological effects. Additionally, during this pandemic, children who are being treated with specific medications (such as immunosuppressant therapy) or who have specific neurological illnesses must be closely watched. The primary drug-drug interactions as well as the neurological adverse effects of COVID-19 therapies should be understood by neurologists.

Von Oertzen et al. [15] presented the following consensus statements from the European Academy of Neurology (EAN) experts for guiding neurologists caring for patients with COVID-19:

- Special precautions to prevent potential exposure to or contamination with SARS-CoV-2 should be taken without postponing treatment while treating acute stroke patients with endovascular therapy.
- The patient or caregiver should get in touch with the homecare/palliative team/caring ALS center and notify the doctor who regularly treats the patient in the event that respiratory decompensation occurs in patients with neuromuscular disorders, such as amyotrophic lateral sclerosis (ALS), who are on home

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ventilatory support or with initial respiratory symptoms.

- For a protracted duration of isolation, a sufficient supply of medication and ventilatory support equipment must be guaranteed.
- When conducting neurophysiology tests, technicians must follow all regulations set forth by the intensive care unit (ICU) medical staff, including those pertaining to droplet and airborne precautions.
- If electroencephalographic (EEG) and electromyographic (EMG) investigations are required, special sanitary settings (in accordance with contamination prevention guidelines) must be set up.
- In order to identify neurological signs and problems, neurologists must be involved in the care of COVID-19 patients from the beginning and in the intensive care unit.
- When a teleconsultation option is available, specialist consultations should be conducted over the phone. This may make it easier to determine which people require in-person appointments.
- Since the effects of respiratory infections are anticipated to be more severe than in the general population, patients with neuromuscular illnesses that specifically affect respiratory function (e.g., ALS) should be quarantined in their homes to prevent contracting the infection.
- Departments are urged to delay any elective EEG and EMG examinations unless they are urgent or likely to significantly alter management, given the lack of personal protective equipment and the potential risk of exposing patients and healthcare workers to infection. However, these choices should be handled in accordance with regional laws and regulations.
- Detergents or products containing alcohol should be used to disinfect wheelchairs, walking aids, and other surfaces. The location where clothing from the outside is collected at the entrance should be included in this as well.
- If necessary, a principal carer should be named; this person will be in charge of coordinating the patient's care. The caregiver should stay beside the patient when they are isolated from others. • If applicable, a backup carer should be identified for each patient, limiting external contacts to reduce the risk of infection.

Several neurological conditions are directly and indirectly affected by COVID-19. To provide a clear and concise summary of these conditions and their relationship with the pandemic, two tables have been organized. Table 1 presents neurological conditions directly affected by COVID-19, detailing the references and the specific impacts of the virus on each condition. Table 2, on the other hand, lists neurological conditions indirectly affected by COVID-19, providing relevant references and explaining how the pandemic has influenced the management and outcomes of these conditions



**Table 1.** Neurological conditions affected by COVID-19 directly.

<b>Condition</b>	<b>Reference</b>	<b>How COVID-19 Affects the Condition</b>
Guillain-Barre Syndrome	[3,4]	Potentially triggered by COVID-19 infection
Encephalitis	[3,10]	SARS-CoV-2 virus can cause encephalitis
Acute Necrotizing Encephalopathy	[4]	Rare complications of COVID-19 infection
Acute Ischemic Stroke	[7,14]	Increased risk due to hypercoagulable state and endothelial dysfunction
Cerebral Venous Thrombosis	[7,11]	Increased risk due to hypercoagulable state
Seizures	[4,8]	Potential association with COVID-19 infection
Myasthenia Gravis	[1,2]	Potential worsening of symptoms due to infection

**Table 2.** Neurological conditions indirectly affected by COVID-19.

<b>Condition</b>	<b>Reference</b>	<b>How COVID-19 Affects the Condition</b>
Multiple Sclerosis	[1,15]	Disruption of routine care and management, potential exacerbation of symptoms
Parkinson's Disease	[9,10]	Disruption of routine care, increased vulnerability to complications from COVID-19
Epilepsy	[1,10]	Disruption of routine care, challenges in emergency management
Alzheimer's Disease	[9]	Disruption of routine care, increased vulnerability to complications from COVID-19, potential cognitive decline

## 7. Treatment of neurological symptoms resulting from long-Covid

Accumulating evidence indicates a high prevalence of prolonged neurological symptoms among COVID-19 survivors [16–19]. Currently, there are no standardized criteria for diagnosing “long COVID” [16,9]. However, long COVID is viewed as a multi-organ disorder with a wide spectrum of clinical manifestations that may indicate underlying cardiovascular, pulmonary, endocrine, hematological, renal, gastrointestinal, dermatological, immunological, psychiatric, or neurological diseases.

Involvement of the central or peripheral nervous system is noted in over one-third of patients who had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with neurological symptoms approximately three times more frequent in observational studies [16,17]. Fatigue, cognitive impairment, headache, sleep, mood, smell or taste disorders, myalgia, sensorimotor deficits, and dysautonomia are the most frequent neurological manifestations of long COVID [16–19]. The pathophysiology underlying long COVID is still unclear, but neuroinflammatory and oxidative stress processes are thought to play a role in propagating long-COVID neurological sequelae [16,18,19].

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Studies have shown that patients with long COVID may demonstrate brain hypometabolism, hypoperfusion of the cerebral cortex, and changes in the brain structure and functional connectivity [18]. Diagnostic and therapeutic algorithms may aid in the prompt recognition and management of underlying causes of neurological symptoms that persist beyond the resolution of acute COVID-19 [16,19]. Collaborative research initiatives are urgently needed to expedite the development of preventive and therapeutic strategies for neurological long COVID sequelae, as causal treatments are currently unavailable [16,19]. Therapeutic approaches are available for symptom-oriented management of neurological long COVID symptoms [16,18].

Early detection and prevention of long-covid neurological sequelae are crucial for the proper long-term management of patients with preexisting neurological diseases. Further research is necessary to elucidate the pathogenesis of long COVID and to establish standardized criteria for its diagnosis [16,19]. The high prevalence of prolonged neurological symptoms among COVID-19 survivors warrants close attention as it may drastically change the traditional treatment of patients with neurological diseases.

## **8. Conclusions**

Critical neurological care during the COVID-19 pandemic is under increasing strain as a result of continuous service reorganization and rationing to address the needs of COVID-19 sufferers. In this article, a number of ideas have been put forth that could reduce the danger to healthcare systems, staff members, and patients with neurological conditions. In addition, public health initiatives need to be taken to inform and raise community awareness of the need for immediate medical assistance in the event of acute neurological symptoms. The pandemic's effects on hospitals necessitate a functional reorganization of all the concerned departments, the formulation of new goals, and the reallocation of resources and responsibilities. Consequently, department employees must be included in this process to ensure they are aware of and accept specific roles. Careful steps need to be taken by the doctors, nurses, and all concerned so that appropriate treatment can be offered to neurological patients during this critical period of time. As more time passes, new challenges stemming from long COVID will need to be understood and treatment of neurological patients adapted accordingly.

In conclusion, it can be said that the COVID-19 storm has presented enormous challenges for neurologists and their patients everywhere in the world. The destruction brought on by the epidemic may have varied greatly depending on the starting points and healthcare systems in each place, but finally, the strength of data sharing, inventiveness, and resiliency won out. "Adaptive neurology" has become the most potent weapon against this invisible foe. Acknowledgments Funding for this paper was provided by Namseoul University

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## Conflict of interest

The author of this paper has declared no conflicts of interest.

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## **Bacterial meningitis-induced demyelination: A logical fallacy or groundbreaking avenue in neuroscience?**

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### **To the Editor,**

Over time, there has been increasing evidence of surviving meningitis patients, especially young adults, having high chances of developing permanent nervous system disability [1]. In this regard, demyelination is hypothesized as one of the emerging pathological mechanisms, since multiple sclerosis (MS), a chronic progressive demyelinating disorder of the central nervous system (CNS), is the most common cause of neurological disability in young adults [2,3]. Linking demyelination with the etiology of meningitis, neuroscientists have long made efforts to discover the pathogenesis of virus induced demyelination, while research on the mechanism of bacteria-induced demyelination is scarce.

On the other hand, a recent study from Ma et al. (2023) asserts that the intraperitoneal injection of the toxin epsilon toxin (ETX), which is made by the gut microbiota member *Clostridium perfringens*, causes demyelination in the corpus callosum, thalamus, cerebellum, brainstem and spinal cord in mice, with an experimental autoimmune encephalomyelitis (EAE) model [4]. This finding has been supported by another study which described the detailed pathological mechanisms of ETX, including blood-brain barrier (BBB) disruption [5], induction of inflammatory cytokines in brain parenchyma that exacerbates neuroinflammation and, finally, damaging the oligodendrocytes via elevation of extracellular glutamate along with activation of metabotropic type 1 glutamate receptors (mGluR1) and N-methyl-D-aspartate receptor (NMDAR), which results in demyelination [6,7]. The toxin, which belongs to the group of cholesterol-dependent cytolysins (CDCs), is known to share the same properties as other CDCs which belong to meningitis-causing bacteria: damaging cell membranes by pore formation and exhibiting cytotoxic effects on various cells [8]. Thus, these findings raise a question: Does bacterial meningitis also potentially cause demyelination?

We discovered evidence in a larger body of literature to demonstrate that other CDCs from meningitis-causing bacteria have similar mechanisms to ETX which, when employed by ETX, induce demyelination in the CNS, although there is still no direct proof that bacterial meningitis can cause demyelination either *in vitro* or *in vivo*. The brain's glutamate level is altered by pneumolysin (PLY) from *Streptococcus pneumoniae*, the most common etiology of bacterial meningitis, which results in synaptic injury [9]. Additionally, an *in vivo* study in pigs has demonstrated that myelin degradation occurred after *Streptococcus suis* was administered. Suilysin (SLY), the toxin produced by this organism, exhibited high expression *in vivo* and was suspected to be the main culprit of the observed

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pathological event [10]. On the other hand, meningitis-causing bacteria can also activate microglia, while ETX has been reported to only act on oligodendrocytes [11]. However, we should keep an eye on their similarities since the possible pathological mechanisms could be related.

How could this emerging concept impact the hospital clinical setting and academic research? Antibiotics should be used appropriately, and treatments should start at the right time in a clinical setting to stop demyelination from progressing. If the pathogenesis has already been established, a strategic research direction on drug-prospecting studies will be followed by the development of specifically targeted treatment modalities based on the investigated pathogenic processes. We are optimistic that a sound understanding of pathogenesis will be a fruitful avenue to prevent further disabilities for bacterial meningitis patients, which have a significant impact on the patients' quality of life.

### **Use of AI tools declaration**

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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### **Conflict of interest**

The authors declare that there were no financial or commercial ties that might be viewed as potential conflicts of interest with this manuscript.

### **Author contributions**

TIP, NMS and AARS were involved in overall structure and elaboration of concepts for review. Manuscript writing was by TIP and NMS. All authors contributed to editing of the manuscript.

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# Marijuana's potential in neurodegenerative diseases: an editorial

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Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), represent a significant global health challenge. These conditions are characterized by the progressive deterioration of neurons in the central nervous system, leading to debilitating symptoms and a decline in cognitive and motor functions. Despite extensive research, effective treatments that can halt or reverse disease progression remain elusive. In recent years, there has been increasing interest in exploring the potential role of marijuana in the management and treatment of neurodegenerative diseases [1]. Inspired by the Special Issue, "Special Edition on Marijuana" of AIMS Neuroscience, we would like to provide a thoughtful perspective on marijuana's potential and its implications in the field of neurodegenerative research.

Marijuana is a plant that contains numerous chemical compounds, with two primary constituents gaining significant attention: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is known for its psychoactive properties such as hypolocomotion, hypothermia, catalepsy, and analgesia. On the other hand, THC has neuroprotective, antispasmodic, and anti-inflammatory actions, which are mediated through the activation of different receptors, such as CB2 and PPAR $\gamma$  [2,9]. Until recently, most of the interest in medical uses of marijuana was focused on the actions of THC, but now there is growing interest in potential medical uses of CBD, which does not have the psychoactive effects of THC and appears to have a number of therapeutic benefits. Other cannabinoids and terpenes present in marijuana contribute to its diverse pharmacological profile, potentially influencing its effectiveness in neurodegenerative diseases. Understanding the composition and interactions of these compounds is crucial in assessing marijuana's therapeutic potential [2].

Interestingly, emerging evidence suggests that marijuana and its constituents possess neuroprotective properties. Cannabinoids, through their interaction with the endocannabinoid system, have demonstrated anti-inflammatory, antioxidant, and anti-excitotoxic effects, which may help combat the underlying mechanisms of neurodegeneration. Preclinical studies have shown promising results, indicating that marijuana-based compounds can protect neurons from damage, promote neuronal survival, and enhance neuroplasticity. These findings warrant further investigation to elucidate the precise mechanisms and translate them into effective clinical interventions [3].

Furthermore, clinical studies evaluating marijuana's effects on neurodegenerative diseases are limited but have shown promising results. In Alzheimer's disease, cannabinoids have exhibited potential in



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reducing neuroinflammation, improving cognitive function, and modulating neurogenesis [4]. In Parkinson's disease, marijuana-based treatments have demonstrated benefits in alleviating motor symptoms, improving sleep quality, and enhancing overall quality of life [5]. Preliminary studies in Huntington's disease and ALS have also indicated potential therapeutic effects, although more research is needed [6]. These findings highlight the need for robust clinical trials to establish marijuana's efficacy, optimal dosage, and long-term safety profile.

While marijuana shows promise, several challenges need to be addressed. The legal and regulatory landscape surrounding marijuana poses barriers to conducting clinical trials and implementing standardized treatment approaches [7]. Additionally, the potential side effects, drug interactions, and variations in individual responses to marijuana-based treatments require careful consideration [8]. Furthermore, the development of targeted therapies based on specific neurodegenerative disease subtypes and stages demands a deeper understanding of the complex pathophysiology of each condition. Moving forward, collaborative efforts involving researchers, clinicians, policymakers, and patients are essential to advance our understanding of marijuana's role in neurodegenerative diseases. Large-scale clinical trials with rigorous methodologies are needed to evaluate the safety, efficacy, and long-term effects of marijuana-based treatments. Standardization of formulations, dosages, and delivery methods is crucial to ensure consistent and reliable outcomes. Additionally, innovative approaches such as precision medicine and personalized treatment strategies may help optimize the implementation of marijuana-based therapies based on individual patient characteristics and disease progression.

The potential role of marijuana in neurodegenerative diseases is a topic that warrants careful consideration and further investigation. And, we believe this special issue of AIMS Neuroscience is one the perfect venues to spark evidence-based discussion on this topic. While the current scientific evidence is promising, more research, including well-designed clinical trials, is needed to establish marijuana's efficacy, safety, and optimal usage in the treatment of neurodegenerative conditions. Collaborative efforts between researchers, healthcare professionals, regulatory bodies, and patients are crucial in advancing our understanding and exploring the full potential of marijuana based therapies. By embracing rigorous scientific exploration, we can unlock new possibilities and potentially improve the quality of life for individuals living with neurodegenerative diseases. However, it is essential to balance the excitement surrounding marijuana's potential with responsible and evidence-based approaches to ensure safe and effective treatments in this complex field.

### **Conflicts of interest**

The author has no conflicts of interest to declare.

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