THE NEUROBIOPHYSICS OF LIFE AND MIND

Editor
NİZAMETTİN DALKILIÇ

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Introduction

Epilepsy-related deaths are most commonly attributed to SUDEP. Neurologist Lina Nashef initially described it as an "unexpected, sudden, witnessed or unwitnessed, non-traumatic, non-

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drowning death in individuals with epilepsy, possibly accompanied by seizures, and not resulting from documented status epilepticus (SE), for which no toxicological or anatomical cause of death could be identified through post-mortem examination" (Nashef, 1997). Epilepsy in young adults (ages 20-45) is associated with a significantly increased risk of SUDEP, estimated to be as high as 27 times greater than in the general population of the same age group (Giussani et al., 2023; Holst et al., 2013). The American Academy of Neurology's guidelines indicate that SUDEP incidence in children is extremely rare at 0.35 per 1000 patient-years, but much higher in adults at 6 per 1000 patient-years, as reported in Harden et al. (Harden et al., 2017b).

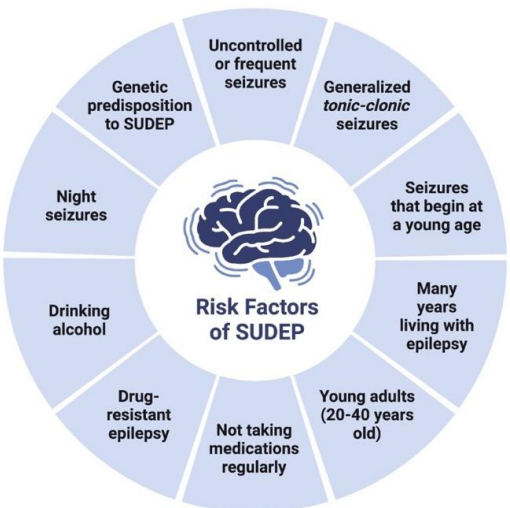
The underlying cause of SUDEP has yet to be clearly identified, despite growing awareness of the condition and its associated risk factors (Fig. 1). Research indicates that cardiac and respiratory function issues associated with seizures may be crucial in the development of SUDEP (Bosch, Sander, & Thijs, 2024; Stöllberger & Finsterer, 2004). Terminal cardiac arrhythmia is commonly cited as the cause of death in SUDEP cases, yet post-mortem examinations fail to reveal structural cardiac problems that would indicate a pathological reason for the death (Pérez-Pérez, Frías-Soria, & Rocha, 2021; Surges, Thijs, Tan, & Sander, 2009). Abnormalities in cardiac electrical activity, including long QT syndrome (LQTS), can lead to adverse autopsy findings, suggesting a possible mechanistic connection between SUDEP and cardiac arrhythmias.

The severity and frequency of generalized tonic-clonic seizures (GTCS) are the most significant risk factors for SUDEP, according to Harden et al. (Harden et al., 2017b). The risk of SUDEP is 15-fold greater in patients experiencing N3 GTCS seizures on a monthly basis (Harden et al., 2017a). Early onset of epilepsy, the use of certain antiepileptic drugs (AEDs), polytherapy, the duration of

epilepsy, and symptomatic causes are further considered risk factors (Whitney & Donner, 2019). Several clinical features, including frequent changes in the dosage of anti-epileptic drugs (AEDs), consistently low plasma levels of AEDs, and poor adherence to medication regimens, have been recognised as primary risk factors for SUDEP (Téllez-Zenteno, Ronquillo, & Wiebe, 2005). Furthermore, these characteristics are frequently observed in patients suffering from refractory epilepsy (RE) (Pérez-Pérez et al., 2021).

The molecular processes underlying epilepsy's potential impact on cardiac function remain poorly understood. Epilepsy-related cardiac dysfunction is a multifaceted issue that may be linked to SUDEP, a significant cause of mortality in individuals with epilepsy. Changes in the functioning or expression of ion channels that adjust the excitability of both brain and heart cells are considered key factors contributing to cardiac problems in people with epilepsy. The review establishes the presence of a shared cardiac characteristic that has relevance across various forms of epilepsy and sheds light on the molecular cause behind cardiac issues in epilepsy.

Figure 1. *Risk factors of SUDEP. BioRender was also created.*



HCN Channels

Seizures typically impact heart rate and rhythm due to autonomic neuronal dysfunction, resulting in substantial negative effects on heart function over time following recurrent seizures, and may ultimately lead to severe clinical outcomes. Individuals with drug-resistant temporal lobe epilepsy experience greater cardiovascular abnormalities compared to those with controlled TLE as observed in the study by Ansakorpi et al. (Ansakorpi et al., 2002). This discovery aligns with the occurrence of recurrent and intense generalized tonic-clonic seizures, which are known risk factors for SUDEP (Surges et al., 2009; Sveinsson, Andersson, Carlsson, & Tomson, 2023). Around 40% of individuals with drug-resistant epilepsy have exhibited one or more cardiac function abnormalities, as noted in a study by Nei et al. (Nei, Ho, & Sperling, 2000). Additionally, heart rate variability is considered a significant indicator of autonomic dysfunction, with numerous studies highlighting epilepsy-related changes in autonomic function in patients with epilepsy (Dono et al., 2022; Sevcencu & Struijk, 2010). Partial and generalized seizures can impact autonomic function at three distinct times: during a seizure (ictal), following the seizure (postictal), and between episodes (interictal), with potential consequences for cardiac arrhythmias.

Abnormalities in cardiac repolarization resulting in ventricular fibrillation have been noted in patients with epilepsy. The duration of ventricular depolarization and repolarization is measured by the QT interval on an electrocardiographic (ECG) recording, with shortening or prolongation of the QT interval being well-documented risk factors for cardiac arrhythmias and sudden cardiac death (Kessi et al., 2022). A temporarily prolonged corrected QT (QTc) interval has been documented to occur in close proximity to seizures in 10-13% of cases, as reported by Brotherstone et al. (Brotherstone, Blackhall, & McLellan, 2010). A shortened QTc

interval has been linked to generalized tonic-clonic seizures (Teh, Tan, Loo, & Raymond, 2007).

The molecular processes that contribute to epilepsy's impact on cardiac function remain poorly understood. A prime candidate for an epilepsy-related acquired cardiac channel disorder is the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, which has been linked to the dual pathologies of epilepsy and cardiac malfunction. Changes in HCN expression and function in the brain have been associated with human epilepsy cases, as reported by Bender et al. (Bender et al., 2003) and also observed in animal models of both genetically and acquired epilepsy, as noted by Kuisle et al. and Powell et al. (Kuisle et al., 2006; Powell et al., 2008). The inward depolarizing current linked to HCN channels, referred to as I_h in the brain and I_f in the heart, is significant in the production and regulation of spontaneous electrical activity in the sinoatrial node in the heart (DiFrancesco, 2010) and in thalamocortical relay neurons in the brain (Pape, 1996). The primary isoforms expressed in the heart are HCN2 and HCN4 (Ou, Niu, & Ren, 2010). Studies show that different parts of the heart express unique patterns of HCN proteins; specifically, HCN4 is predominantly found in the sinoatrial node while HCN2 is mainly expressed in both atrial and ventricular muscle cells (Ou et al., 2010). HCN channels are crucial for the heart's proper functioning, and research involving HCN-deficient mice provides substantial evidence to support this. Mice lacking HCN2 exhibit a complex condition featuring seizures and irregular heart rhythms (Ludwig et al., 2003) whereas mice with a global or heart-specific deficiency in HCN4 die in the womb due to an inability to form functional sinoatrial pacemaker cells (Stieber et al., 2003). Moreover, conditional deletion of HCN4 in adulthood results in a significant reduction (~75%) in sinoatrial If and cardiac arrhythmias characterized by recurring sinus pauses (Herrmann, Stieber, Stöckl, Hofmann, & Ludwig, 2007). Studies in mice have

been consistent with four distinct mutations in the human HCN4 gene that result in modified channel expression and/or physical properties and are linked to sinus bradycardia and complex cardiac arrhythmia (Milanesi, Baruscotti, Gnecchi-Ruscone, & DiFrancesco, 2006; Schulze-Bahr et al., 2003).

Ionic currents that are dependent on voltage encompass the Na^+ current (Baruscotti, DiFrancesco, & Robinson, 1996) L- and T-type Ca^{2+} currents (Ono & Iijima, 2005), HCN I_f current (DiFrancesco, 2010) and various delayed rectifier K^+ currents (Ono & Ito, 1995). There is still some disagreement about the precise impact of various ion channels on sinoatrial node pacing, but scientists now largely concur that the I_f current is crucial in shaping and regulating pacemaker activity as stated in DiFrancesco (DiFrancesco, 2010). HCN channels and the I_h current also influence neuronal excitability in the brain, and studies have identified changes in HCN channel expression and function in patients with epilepsy (Bender et al., 2003) as well as in animal models of epilepsy (Kuisle et al., 2006; Powell et al., 2008). Mutations in the HCN2 and HCN4 genes have been found in SUDEP victims, suggesting that these channels may be involved in the development of life-threatening heart arrhythmias in people with epilepsy (Tu, Waterhouse, Duflou, Bagnall, & Semsarian, 2011).

Consistent molecular and cardioelectrophysiological findings have been observed across both epilepsy models, despite their distinct causes and seizure types. These models exhibited downregulation of HCN channels, particularly the HCN2 isoform, and similar cardiac anomalies, including prolonged QT intervals and heightened heart rate variability. The prolonged QTc interval is a characteristic of "long QT syndrome," a potentially life-threatening arrhythmia caused by mutations in ion channels, which can lead to a heightened risk of ventricular tachyarrhythmias and sudden death (Crotti, Celano, Dagradi, & Schwartz, 2008). The discovery of

longer QTc intervals in epileptic rats suggests that this could also be a contributing factor in SUDEP cases among humans with epilepsy. Reports of prolonged QTc intervals have been documented in patients with chronic drug-resistant epilepsy who underwent video-EEG and cardiac monitoring simultaneously (Brotherstone et al., 2010) as well as in patients with epilepsy who later died from SUDEP (Tavernor, Brown, Tavernor, & Gifford, 1996).

Inward rectifier potassium (Kir) channels

Research conducted in both clinical and experimental settings has demonstrated an impact of epilepsy on cardiac function. The molecular process underlying this phenomenon remains unclear. Statistics indicate that roughly 2% of the global population suffers from epilepsy, yet the underlying reason for substantial treatment resistance remains unclear, despite substantial progress in therapy. SUDEP is a major contributor to mortality among drug-resistant young adults, and according to Yang et al. (Yang et al., 2018), approximately 40% of these patients exhibit one or more anomalies in cardiac function. Furthermore, fluctuations in heart rate are a significant indicator of autonomic dysfunction, and numerous studies have demonstrated autonomic changes in individuals with chronic epilepsy.

Kir channels, which facilitate the movement of K^+ ions to cells such as neurons and cardiomyocytes, are put forward as a potential mechanism; they modulate cell excitability by influencing the repolarization phase of the cardiac action potential (Cui, Cantwell, Zorn, & Logothetis, 2021; Massey, Sowers, Dlouhy, & Richerson, 2014). Speculation exists that dysfunction of Kir channels is a contributing factor to epileptic seizures, despite these channels having a buffer system within glial cells, thereby making it relatively easy to compensate for seizures, allowing patients with epilepsy to maintain their normal lives (Akyuz, Koklu, Uner,

Angelopoulou, & Paudel, 2022; Grant, 2009). Apparently, dysfunctional Kir channels may contribute to cardiac issues and SUDEP in epilepsy patients towards the end of their life, primarily because the heart lacks a mechanism to regulate extracellular potassium levels (Köhling & Wolfart, 2016). A small difference in concentration may be the primary reason for the lethal outcome. Kir channel expression in cardiac tissue has been identified as a possible mechanism to explain cardiac pathology in epilepsy, a notion previously supported by research showing altered Kir channel expression in epileptic brains (Baculis et al., 2017).

Studies were conducted using the PTZ-kindling model in rats (Wong et al., 2015) to show that Kir channels are crucial in the SUDEP mechanism, by examining their expression in heart tissue affected by epilepsy (Auzmendi, Akyuz, & Lazarowski, 2021; Wong et al., 2015). Subsequent studies revealed that the autonomic nervous system was profoundly impacted by electrocardiogram recordings and blood pressure monitoring, leading to a decrease in the duration of the ST segment in epileptic rats (Wong et al., 2015). Predictions had indicated that Kir2.x channels, which are involved in the repolarization phases of the cardiac action potential, would be affected; molecular analysis revealed a substantial decrease in cardiac Kir channel mRNA and protein expression in rats given PTZ. Notably, both Kir2.x, which facilitates I_{K1} efflux in ventricular tissue, and Kir3.x, responsible for I_{KACh} in the atrium, underwent significant reductions in this study (Wong et al., 2015).

Sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA)

The cytosolic calcium concentration when the cell is at rest is maintained at approximately 10,000 times lower levels than those found outside the cell. Intracellular calcium levels are regulated by the removal of excess calcium to the surrounding extracellular environment, or by its storage within specific intracellular

organelles, including the endoplasmic reticulum (ER) and mitochondria. The regulation of intracellular calcium levels relies on energy-dependent processes. The plasma membrane is equipped with calcium ATPase, and sodium-calcium exchangers remove calcium ions at the expense of the sodium gradient produced by sodium-potassium ATPase. Calcium enters the endoplasmic reticulum through SERCA activity or into mitochondria, which requires the maintenance of a proton gradient across the inner mitochondrial membrane. Disruptions to mechanisms for eliminating Ca^{2+} or loading calcium into cells can lead to an excessive amount of intracellular calcium, potentially resulting in cell death (Paschen, 2003).

Disruptions in the balance of calcium in brain cells are linked to several neurological disorders, including stroke, low blood sugar, and epilepsy (Kahlert & Reiser, 2004; Yao & Haddad, 2004). Cell death linked to these conditions is caused by an excitotoxic process triggered by the activation of N-methyl-D-aspartate (NMDA) glutamate receptors, which have a high permeability to calcium ions (Mayer & Westbrook, 1987); (Arundine & Tymianski, 2003). Excessive calcium leads to the overactivation of several signals, like proteases, phospholipases, and DNAses, which contribute to cell death as stated by Siesjö, Hu, & Kristian (Siesjö, Hu, & Kristìan, 1999). Mitochondrial involvement in excitotoxic cell death has become a significant area of focus more recently. Mitochondrial calcium overload triggers a series of events including the depolarization of the mitochondrial membrane, the production of reactive oxygen species, the opening of the mitochondrial permeability transition pore, depletion of ATP, and ultimately leads to the release of cytochrome C and the activation of caspase (Vesce, Kirk, & Nicholls, 2004).

Less emphasis has been placed on the ER's role in Ca^{2+}-mediated neuronal death; nonetheless, it has been proposed that

prolonged ER depletion of Ca^{2+} is a vital factor in neuronal injury (Paschen & Doutheil, 1999). Research indicates that the role of intracellular Ca^{2+} pools in excitotoxic cell death can be attributed to the protective properties of dantrolene, a ryanodine receptor (RyR) antagonist, which mitigates neuronal damage caused by NMDA (GepdIremen, Düzenl, Hacimüftüoğlu, Süleyman, & Oztaş, 2001), ischemia (Nakayama, Yano, Ushijima, Abe, & Terasaki, 2002) and oxygen - glucose deprivation (Wang, Nguyen, Maguire, & Perry, 2002). Antagonists of phospholipase C-dependent metabotropic glutamate receptors are found to prevent hypoxic-mediated death in hippocampal cultures (Opitz & Reymann, 1991). The results indicate that intracellular calcium reserves within the endoplasmic reticulum are involved in excitotoxicity.

T-Type Ca^{2+} Channels

Seizures in patients with epilepsy have been shown to cause autonomic neuronal dysfunction, and they can also impact heart rate and rhythm. Moreover, recurrent seizures can impair heart function, potentially resulting in severe clinical consequences (Jansen & Lagae, 2010). Investigations into the cardiovascular system have been conducted as a result of cardiac arrhythmias being one of the possible reasons for SUDEP (Velagapudi, Turagam, Laurence, & Kocheril, 2012). Research into the effects of epilepsy on the cardiovascular system has been extensive, yet few studies have specifically investigated cardiovascular functions in individuals with absence epilepsy or in lab animals with absence epilepsy. Absence epilepsy, typically manifesting in childhood, is a neurological disorder defined by spike-wave discharges (SWDs) indicating spontaneous recurrent seizures on electroencephalogram (Depaulis & Charpier, 2018). The WAG/Rij and GAERS rat strains serve as reliable genetic animal models for absence epilepsy (Depaulis & Charpier, 2018). The seizures observed in these rats are remarkably similar to human absence seizures in terms of EEG readings,

observed behaviors, and reactions to antiepileptic medication (van Luijtelaar & Depaulis, 2006).

Up to now, research employing animal models of absence epilepsy has concentrated on the part that GABAergic neurotransmission plays in central cardiovascular control. Research in WAG/Rij and GAERS rats has demonstrated that GABAergic inhibition, especially in the amygdala and hypothalamus, has a significant impact on the regulation of mean arterial blood pressure and heart rate (Yananli et al., 2008). Research has found that cardiac electrophysiological alterations occurred in GAERS rats, resulting from a lower heart rate, and this was attributed to reduced expression of cardiac HCN channels (Powell et al., 2014). Despite an extensive review of the literature, no study has been found to report any impairment of vascular reactivity in animals with absence epilepsy. Studies have demonstrated the thalamocortical network's significant role in the development and progression of spike-wave discharges (SWDs), which can be observed in patients with absence seizures as well as in various animal models of absence epilepsy (Crunelli & Leresche, 2002). T-type Ca^{2+} channels, which influence neural firing and the creation of neuronal oscillations (Perez-Reyes, 2003), are particularly abundant in the thalamocortical circuit (Cheong & Shin, 2013). Previous research has demonstrated that mice lacking T-type Ca^{2+} channels are resistant to SWD formation as a result of pharmacological treatment (Kim et al., 2001) and overexpression of the T-type Ca^{2+} channel results in mice displaying the characteristic absence phenotype (Ernst, Zhang, Yoo, Ernst, & Noebels, 2009; Torrente, Mesirca, Bidaud, & Mangoni, 2020).

According to previous studies, WAG/Rij rats show the initial presence of first SWDs in their cortical EEG recordings at the age of 2 months (Fedosova et al., 2014). Previous studies have found no notable variation in mean arterial blood pressure between mice lacking T-type Ca^{2+} channels and normal controls (Harraz et al.,

2015; Svenningsen et al., 2014). Research indicates that T-type Ca^{2+} channels exert no direct influence on the regulation of blood pressure. One study found that mice without Cav3.1 T-type Ca^{2+} channels had a reduced heart rate, implying that Cav3.1 T-type Ca^{2+} channels could be involved in controlling heart rate by influencing pacemaker activity and atrioventricular conduction (Mangoni et al., 2006). Research has also indicated that mice without Cav3.1 T-type Ca^{2+} channels experience slower heart rates without any variation in mean arterial blood pressure (El-Lakany et al., 2023; Svenningsen et al., 2014).

This phenomenon may be attributed to reflex bradycardia compensating for increased peripheral vascular resistance. The rise in mean arterial blood pressure in WAG/Rij rats could be attributed to a compensatory response to environmental stress or the lack of seizures seen in this particular genetic model. Further investigation is required to understand the reasons behind the elevated mean arterial blood pressure levels observed in WAG/Rij rats. It is widely acknowledged that the presence of carbachol or acetylcholine in an intact endothelium results in endothelium-dependent vasorelaxation through the activation of the NO/cGMP pathway in precontracted vascular smooth muscle cells, which have been constricted by agents such as norepinephrine, potassium, or phenylephrine (Furchgott, 1983).

Furthermore, the cardiovascular centre is crucial in the neural control of blood pressure. In contrast, thoracic aortas do not directly mirror peripheral resistance due to their size as large vessels. As a result, the previously mentioned factors can influence blood pressure in WAG/Rij rats. Research indicates the existence of two subtypes of T-type Ca^{2+} channels, specifically Cav3.1 and Cav3.2, within the vascular structure (Hansen, 2013) and it has been proposed that these channels play a role in the excitation-contraction process in rodent and human blood vessels (Hansen et al., 2011). T-type Cav3.1

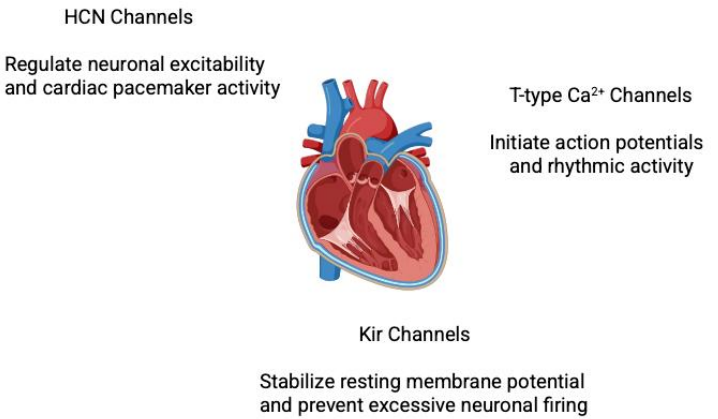
channels coexist with eNOS in the endothelium of mouse mesenteric arteries and directly stimulate eNOS, thereby facilitating NO synthesis (Svenningsen et al., 2014). No significant difference was observed between mice lacking Cav3.1 channels and normal controls in their acetylcholine-induced relaxation responses. The inconsistent findings in this situation may be attributed to multiple factors.

Conclusion

Understanding SUDEP requires knowledge of the roles HCN channels, T-type Ca^{2+} channels, and Kir channels play in its underlying mechanisms, as Fig. 2 illustrates. HCN channels also have a crucial role in controlling both neuronal excitability and the activity of the heart's pacemaker. Their hyperpolarization-activated properties enable them to contribute to the resting membrane potential and the generation of rhythmic activity in both neurons and cardiac muscle cells. Disruption of HCN channels may cause irregular neuronal firing patterns and impaired cardiac autonomic regulation, thereby elevating the risk of arrhythmias during or after seizures. Modulating HCN channel activity may offer a potential therapeutic target for reducing the risk of SUDEP. Calcium channels found in the T-type category are essential for the development of low-threshold calcium spikes, which are vital for neurons to start action potentials, and also play a part in pacemaker activity within cardiac tissues. Aberrant activation of T-type calcium channels in epilepsy leads to heightened neuronal excitability and facilitates seizure spread. Their participation in heart function implies that the malfunction of these channels could lead to the irregular heartbeat seen in SUDEP cases. Targeting T-type calcium channels may offer a dual benefit in managing both seizure activity and associated cardiac risks. Inward rectifier potassium channels, classified as Kir channels, play a crucial role in preserving the resting membrane potential and controlling excitability in both neurons and cardiac

cells. During hyperpolarization, these mechanisms enable the influx of potassium, maintain a stable membrane potential, and prevent overactive neuronal firing. Impaired Kir channel function in the context of SUDEP may result in heightened neuronal excitability and an elevated risk of seizure-induced cardiac dysregulation. Stabilizing neuronal and cardiac function via enhanced Kir channel activity may lower the risk of SUDEP.

Figure 2. *General characteristics of HCN channels, T-type Ca^{2+} channels and Kir channels. BioRender was also created.*



The collective contribution of HCN, T-type Ca^{2+} channels, and Kir channels helps maintain the intricate balance of neuronal excitability and cardiac function. The abnormal functioning of these channels is thought to contribute substantially to the underlying causes of SUDEP, underscoring the need for further investigation into their mechanisms. Clarifying the dynamics of these interactions could potentially lead to the development of new treatment approaches designed to decrease the likelihood of SUDEP by focusing on these particular ion channels to re-establish normal excitability and cardiac rhythm regulation.

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FRONTOTEMPORAL DEMENTIA: A DISTINCT CLINICAL and MOLECULAR ENTITY in the SPECTRUM of NEURODEGENERATIVE DISEASES

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Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder that predominantly affects individuals under 60, presenting with behavioral, language, and motor deficits. Behavioral features often include apathy, disinhibition, compulsive behaviors, and loss of empathy, significantly impairing social functioning and daily life (Mollah et al., 2024; Finger et al., 2016; Woollacott et al., 2016; Olney et al., 2017; Peet et al., 2021). The clinical spectrum includes behavioral variant FTD (bvFTD), semantic and non-fluent variants of primary progressive aphasia (svPPA, nfvPPA), motor neuron disease, progressive supranuclear palsy, and corticobasal syndrome (Olney et al., 2017; Peet et al., 2021). Although traditionally considered an early-onset dementia, epidemiological studies show that incidence increases with age,

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peaking between 71–79 years (Leroy et al., 2021; Logroscino et al., 2019), with lifetime risk estimates ranging from 1 in 400 to 1 in 742 (Coyle et al., 2016; Logroscino et al., 2019).

Building on this clinical and epidemiological framework, genetic contributions are particularly prominent in FTD. Genetic factors account for a substantial proportion, with 20–50% of cases familial and approximately 30% showing a strong family history (Greaves et al., 2019; Olszewska et al., 2016; Moore et al., 2019). Autosomal dominant mutations in C9orf72, GRN, and MAPT account for most inherited cases, with C9orf72 being the most common cause (Greaves et al., 2019; Olszewska et al., 2016; Moore et al., 2019; Wagner et al., 2021; Mol et al., 2020). These three genes explain about 60% of familial FTD, while rarer variants in TBK1, VCP, CHMP2B, TARDBP, and FUS constitute <5% (Greaves et al., 2019; Olszewska et al., 2016; Wagner et al., 2021; Mol et al., 2020; Kirola et al., 2022; Jiang et al., 2021). Autosomal dominant inheritance is present in one-third to one-half of familial FTD, corresponding to 1–5% of all FTD cases (Greaves et al., 2019; Olszewska et al., 2016). Age at onset and disease duration vary with gene, mutation, and family background (Moore et al., 2019). Additionally, immune-related factors and polygenic risk contribute, with evidence of shared loci across neurodegenerative diseases (Broce et al., 2018; Ferrari et al., 2016; Kirola et al., 2022).

Beyond genetic susceptibility, environmental exposures have also been implicated in shaping disease risk. Traumatic brain injury (TBI) is a strong factor, with studies reporting odds ratios up to 3.3 and hazard ratios of 4.43 (Rosso et al., 2003; Wang et al., 2015). A dose-dependent effect has been observed, where repeated head trauma or contact sports increase severity and lead to earlier onset (Asken et al., 2024; Soppela et al., 2022). Animal models support these findings, linking TBI to FTD-like pathology with TDP-43

abnormalities (Wang et al., 2015). Thyroid dysfunction has also been suggested as a risk factor, though evidence is inconclusive (Rosso et al., 2003). Thus, head trauma is a well-established modifiable risk factor, whereas the role of thyroid dysfunction remains uncertain (Rosso et al., 2003; Asken et al., 2024; Soppela et al., 2022; Wang et al., 2015).

Given these diverse risk determinants, clinical expression of FTD is highly heterogeneous. bvFTD often manifests as personality change, disinhibition, apathy, and social withdrawal, while PPA variants cause progressive language decline (Olney et al., 2017). FTD-ALS cases show rapid progression and severe motor involvement (Logroscino et al., 2023). Misdiagnoses are common, often confused with psychiatric disorders or Alzheimer's disease, delaying management (Woolley et al., 2011; Ducharme et al., 2020). Prognosis varies: FTD-ALS typically leads to survival of 2–3 years, whereas svPPA can extend to 12 years (Su et al., 2021; Tan et al., 2019). ALS features nearly triple mortality risk in FTD patients (Su et al., 2021). These distinctions underscore the need for accurate clinical and imaging assessments (Omer et al., 2017; McKenna et al., 2021).

Prognostic variability directly underscores the need for early and accurate subtype classification. Emerging therapies highlight the importance of timely diagnosis for personalized care and clinical trial enrollment (Rabinovici & Miller, 2010; Boxer et al., 2020). Advances in molecular genetics have revealed diverse underlying pathologies and significant overlap with psychiatric disorders, complicating diagnosis (Leyton et al., 2010; Liscic et al., 2009; Boxer et al., 2020).

An illustrative case of this complexity is bvFTD, the most frequent very early-onset subtype. It is associated with heterogeneous proteinopathies, including tau pathology linked to

MAPT mutations, as well as TDP-43 and ubiquitin-positive inclusions (Mann & Snowden, 2017; Ohm et al., 2024; Santillo et al., 2022). Biomarker studies show tau and TDP-43 are detectable in plasma and cerebrospinal fluid, aiding subtype distinction (Chatterjee et al., 2024; Remnestål et al., 2020; Rohrer et al., 2016). Imaging and molecular analyses reveal tau-driven bvFTD presents with selective pyramidal neuron loss, while TDP-43 pathology shows broader degeneration (Kubota et al., 2025; Shen et al., 2023). Non-fluent and semantic PPA variants are also strongly associated with TDP-43 pathology (Mann & Snowden, 2017). These findings emphasize the importance of molecular diagnostics for accurate classification and therapy development (Chatterjee et al., 2024; Kubota et al., 2025).

While some cases are sporadic, the high familial aggregation in early-onset FTD highlights its strong genetic basis. Neuropathologically, FTD is classified into tauopathies, TDP-43 proteinopathies, and FET proteinopathies (Mackenzie & Neumann, 2016). This classification has enhanced understanding of molecular mechanisms. Genetic and proteomic studies suggest biomarkers for early detection and monitoring (Leyton & Hodges, 2010). Experimental therapies, including antisense oligonucleotides for C9orf72 and GRN mutations and immunotherapies targeting protein aggregates, are under development (Wang et al., 2013).

Despite these promising developments, major challenges remain. Biomarker development is still limited, and no disease-modifying treatments are approved. The genetic heterogeneity of MAPT, GRN, and C9orf72 mutations underscores the need for tailored therapies (Benussi & Borroni, 2023). Research remains dominated by Western cohorts, highlighting the need for globally inclusive studies (Franzen et al., 2023). The molecular roles of tau and TDP-43 remain incompletely understood, complicating targeted

intervention (D'Alton & Lewis, 2014). Overall, despite advances, FTD's clinical and molecular complexity continues to demand standardized diagnostics, effective therapies, and more diverse research approaches.

To provide a comprehensive understanding of this complex disorder, the following sections of this chapter will first examine the genetic and environmental determinants of FTD, then address the clinical variability and diagnostic challenges across its subtypes, and finally explore the molecular pathogenesis and emerging therapeutic strategies. This structured approach aims to integrate epidemiological, clinical, and molecular perspectives to inform future diagnostic and therapeutic developments.

Genetic and Environmental Determinants of Frontotemporal Dementia

Frontotemporal dementia (FTD) has a substantial heritable component, with approximately 20–50% of cases demonstrating familial aggregation and around 30% showing a strong family history (Greaves & Rohrer, 2019; Olszewska et al., 2016). The majority of inherited cases are linked to autosomal dominant mutations in C9orf72, GRN (progranulin), and MAPT (microtubule-associated protein tau), with C9orf72 expansions representing the most common genetic cause worldwide (Mol et al., 2020; Wagner et al., 2021). These three genes collectively account for nearly 60% of familial FTD, while rarer variants in TBK1, VCP, CHMP2B, TARDBP, and FUS explain a smaller subset (<5%) (Olszewska et al., 2016; Kirola et al., 2022). Beyond monogenic mutations, genome-wide association studies have revealed that FTD is also influenced by polygenic risk and immune-related loci, with overlaps observed across other neurodegenerative conditions such as Alzheimer's and Parkinson's disease (Broce et al., 2018; Ferrari et al., 2016). This highlights a complex genetic architecture where both

rare, high-penetrance mutations and common variants shape disease risk.

Environmental factors also play a pivotal role in modulating FTD onset and progression. Traumatic brain injury (TBI) has been consistently identified as a strong risk factor, with individuals sustaining head trauma demonstrating a significantly elevated likelihood of developing FTD (Rosso et al., 2003; Wang et al., 2015). Recent clinical evidence indicates a dose-dependent relationship, where recurrent trauma or participation in contact sports is associated with earlier symptom onset and accelerated cognitive decline (Asken et al., 2024; Soppela et al., 2022). Experimental studies further support these findings, demonstrating that TBI can trigger neuropathological changes resembling FTD, particularly through mechanisms involving TDP-43 aggregation (Wang et al., 2015). Although less established, thyroid dysfunction has also been proposed as a potential contributor to FTD pathogenesis, though current data remain inconclusive (Rosso et al., 2003).

Collectively, these findings underscore the interplay between genetic predisposition and environmental insults in shaping disease trajectory. Identifying individuals at greatest risk based on genetic background and modifiable exposures remains essential for developing targeted prevention and early intervention strategies in FTD.

Clinical Variability and Diagnostic Challenges Across FTD Subtypes

The clinical spectrum of frontotemporal dementia (FTD) encompasses diverse phenotypes with distinct yet overlapping presentations. Behavioral variant FTD (bvFTD), the most prevalent subtype, is characterized by disinhibition, apathy, compulsive behaviors, and loss of empathy, often leading to profound social and functional impairment (Olney et al., 2017; Woollacott & Rohrer,

2016). In contrast, primary progressive aphasia (PPA) variants, including semantic variant (svPPA) and non-fluent/agrammatic variant (nfvPPA), predominantly affect language, with svPPA presenting as progressive loss of word meaning and nfvPPA characterized by impaired grammar and speech production (Montembeault et al., 2018; Tippett & Keser, 2022). The heterogeneity extends to FTD with motor involvement, particularly FTD-ALS, where patients exhibit more aggressive disease courses and severe motor decline (Su et al., 2021).

Despite advances in clinical characterization, diagnostic challenges persist. FTD symptoms are frequently misattributed to psychiatric conditions such as major depression, schizophrenia, or bipolar disorder, delaying appropriate management and care (Woolley et al., 2011; Ducharme et al., 2020). Neuroimaging approaches, including FDG-PET and structural MRI, have provided valuable insights by identifying region-specific patterns of hypometabolism and atrophy, thereby improving subtype differentiation (Cayir et al., 2024; Ma et al., 2024). Machine learning applications further enhance diagnostic accuracy, allowing more nuanced recognition of overlapping subtypes and disease stages (Metz et al., 2025).

Prognosis varies substantially among subtypes. FTD-ALS is associated with the shortest survival, typically 2-3 years from diagnosis, while svPPA can progress more slowly, with survival extending up to a decade or longer (Tan et al., 2019; Su et al., 2021). Imaging studies demonstrate that cerebellar and infratentorial changes may also contribute to phenotype-specific disease burden (McKenna et al., 2021; Omer et al., 2017). Accurate recognition of these clinical and neuroimaging patterns is therefore essential for prognosis, treatment planning, and counseling of patients and families.

Overall, the marked clinical variability of FTD highlights the importance of integrative diagnostic approaches that combine behavioral assessments, language profiling, advanced imaging, and emerging computational tools. Such strategies will be critical for refining clinical criteria, minimizing misdiagnoses, and supporting timely intervention.

Molecular Pathogenesis and Emerging Therapeutic Strategies

At the neuropathological level, frontotemporal dementia (FTD) is defined by the abnormal accumulation of pathogenic proteins, primarily tau, TDP-43, and FUS, which lead to distinct molecular subtypes known as tauopathies, TDP-43 proteinopathies, and FET proteinopathies (Mackenzie & Neumann, 2016; Mann & Snowden, 2017). Each proteinopathy exhibits characteristic patterns of cortical vulnerability and progression, contributing to the phenotypic heterogeneity observed across FTD subtypes. For example, MAPT mutations frequently result in tau aggregation, while C9orf72 and GRN mutations are strongly associated with TDP-43 pathology (Rademakers et al., 2012; Gao et al., 2017).

Recent advances in molecular imaging have provided valuable insights into FTD pathogenesis. PET tracers allow in vivo visualization of tau burden, facilitating differentiation among FTD subtypes and distinguishing them from Alzheimer's disease (Kubota et al., 2025; Santillo et al., 2022). Similarly, neuroimaging studies show that laminar degeneration in bvFTD is strongly influenced by the underlying molecular pathology, with distinct cytoarchitectonic patterns between tau- and TDP-43-mediated disease (Ohm et al., 2024; Shen et al., 2023). These findings underscore the need to integrate clinical and imaging data with molecular biomarkers for precise diagnosis and prognosis.

Biomarker research has expanded beyond imaging to include cerebrospinal fluid (CSF) and blood-based markers. Altered CSF protein levels, including neurofilament light chain (NfL), tau, and TDP-43, have been consistently associated with disease presence and severity (Abu-Rumeileh et al., 2018; Körtvelyessy et al., 2018; Remnestål et al., 2020). Plasma extracellular vesicle-derived tau and TDP-43 have recently been identified as promising diagnostic biomarkers, with potential utility for distinguishing FTD from ALS and other dementias (Chatterjee et al., 2024). Blood-based biomarker development remains an active field, with growing evidence for panels that combine inflammatory, metabolic, and neurodegenerative markers (Gossye et al., 2019; Liampas et al., 2024).

Emerging therapeutic strategies are increasingly directed at molecular targets. Antisense oligonucleotides (ASOs) aimed at reducing pathogenic C9orf72 repeat expansions or restoring GRN function are under active investigation, alongside immunotherapies targeting tau and TDP-43 aggregates (Wang et al., 2013; Boxer et al., 2020). Modulation of autophagy and RNA metabolism has also been proposed, given their roles in protein clearance and homeostasis (Houghton et al., 2022; Hung & Patani, 2024). Although no disease-modifying treatments are yet approved, advances in precision medicine and biomarker development provide a strong foundation for future targeted interventions (Magrath Guimet et al., 2022).

In sum, the integration of molecular insights, biomarker discovery, and novel therapeutics represents a paradigm shift in FTD research. Continued progress will depend on refining diagnostic tools, validating biomarkers across diverse populations, and translating molecular discoveries into clinically effective therapies.

Conclusions

Frontotemporal dementia (FTD) exemplifies the complexity of neurodegenerative disease, with its interplay of genetic, environmental, clinical, and molecular determinants. Advances in epidemiology and molecular genetics have clarified the roles of key mutations such as C9orf72, GRN, and MAPT, while also highlighting the contribution of rarer variants and immune-related risk factors. Environmental exposures, particularly traumatic brain injury, further shape disease risk and age at onset.

Clinically, the heterogeneity of FTD continues to challenge diagnostic precision. Subtype-specific features, overlapping symptoms with psychiatric disorders, and variable prognoses complicate early recognition and management. Incorporating neuroimaging, machine learning tools, and refined clinical criteria will be essential to reduce misdiagnoses and support individualized care.

On the molecular front, recognition of tau, TDP-43, and FET proteinopathies has reshaped understanding of FTD pathogenesis. The growing arsenal of biomarkers, spanning cerebrospinal fluid, blood, and neuroimaging modalities, promises earlier detection and more accurate stratification of patients. Concurrently, therapeutic innovations-including antisense oligonucleotides, immunotherapies, and approaches targeting protein clearance-represent the most promising avenues toward disease-modifying treatments.

Nevertheless, key gaps remain. The lack of widely validated biomarkers, limited representation of non-Western populations in research, and the absence of approved therapies highlight the urgent need for global, multidisciplinary collaboration. Addressing these challenges will be critical not only for advancing treatment of FTD but also for informing broader neurodegenerative disease research.

In conclusion, FTD represents both a formidable challenge and a unique opportunity: its distinct clinical and molecular features provide a lens through which to refine our understanding of neurodegeneration, develop precision diagnostics, and pioneer targeted interventions that may ultimately transform outcomes for patients and families worldwide.

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NEUROBIOPHYSICAL DYNAMICS of MEMORY and ATTENTION

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Introduction

The brain serves as the core of cognitive functions, controlling learning, memory, and attention, and is organized into a complex network (Kandel, Schwartz, & Jessell, 2013). An approach focusing on the biophysics of these processes offers a neurobiophysical foundation by describing the structural, electrical, and chemical dynamics of neuronal activity (Buzsáki, & Draguhn, 2004). Brain memory is comprised of the processes of encoding learned information, retaining it, and retrieving the stored information. Structures in the medial temporal lobe, including the hippocampus, are crucial for these functions (Squire, & Zola-Morgan, 1991). These processes are influenced by synaptic plasticity and oscillatory activity at the neurobiophysical level, as described by (Bliss, & Lømo, 1973; Fell, & Axmacher, 2011). Attention involves the selection of a specific target for subsequent processing and the

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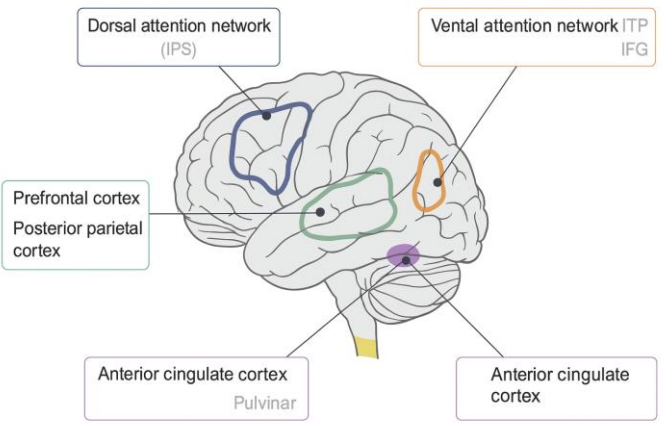
allocation of neural resources to that target. This process also enhances information processing efficiency by allocating resources towards specific stimuli (Posner, & Petersen, 1990). The process is linked to the electrical activity patterns and synchronisation dynamics of cortical networks (Fries, 2009). Attentional processes are influenced by interactions between brain regions like the prefrontal cortex, the parietal lobe, and the thalamus, as noted by Corbetta, & Shulman, (2002). Attention and memory are closely connected and interdependent systems; attention picks out information for processing, whereas memory influences attention based on past occurrences (Awh, Vogel, & Oh, 2006). Information encoded through attentional focus persists longer, and information acquired in the past also influences focus of attention (Chun, & Turk-Browne, 2007). Examining the relationship between memory and attention at the biophysical level is crucial not only for understanding basic neuroscientific systems but also for explaining clinical applications and neurodegenerative disorders (Baddeley, 2012). This study will investigate the functions of key brain areas, including the hippocampus, prefrontal cortex, parietal lobe, and anterior cingulate cortex, in the processes of memory and attention. The examination will also consider how these functions are associated with neuroimaging research and clinical data (Chun, Golomb, & Turk-Browne, 2011). Examples of memory and attention impairments will be used to illustrate clinical implications in neurological and psychiatric disorders.

The Brain's Basis for Attention

Cognitive resources can be focused on particular stimuli through a selective process known as attention, which is controlled by a variety of interconnected brain networks (Posner, & Petersen, 1990). The brain areas involved in attention functions are shown in Figure 1. The dorsal attention network, comprising the intraparietal sulcus (IPS) and frontal eye field (FEF), plays a role in goal-oriented,

top-down control (Corbetta, & Shulman, 2002). The ventral attention network, which includes the temporoparietal junction (TPJ) and inferior frontal gyrus, plays a role in bottom-up reorientation to unexpected or prioritized stimuli (Corbetta, Patel, & Shulman, 2008). This connectivity enables the flexible design of both goal-focused and stimulus-focused attentional stages (Vossel, Geng, & Fink, 2014). The prefrontal cortex is crucial for controlling attention and helps maintain task instructions that guide goal-directed actions (Miller, & Cohen, 2001). The posterior parietal cortex plays a crucial role in spatial orientation and sensory coordination, as indicated by Culham, & Kanwisher, (2001). The anterior cingulate cortex, or ACC, is involved in error detection and conflict resolution, leading to the realignment of attentional resources, a process described by Botvinick, Cohen, & Carter, (2004). Regulating the transfer of attentional information between cortical areas is facilitated by the pulvinar thalamus, enhancing coordination (Saalmann et al., 2012).

Figure 1. Brain areas involved in attention functions



Source: https://doi.org/10.1038/nrn755

Studies involving functional magnetic resonance imaging have found that attentive states are associated with increased

selectivity and amplitude of neuronal responses in the visual cortex (Kastner, & Ungerleider, 2000). Electrophysiological research has demonstrated that stimuli requiring attention improve information processing efficiency by increasing the coordination of the gamma band (Fries, 2009).

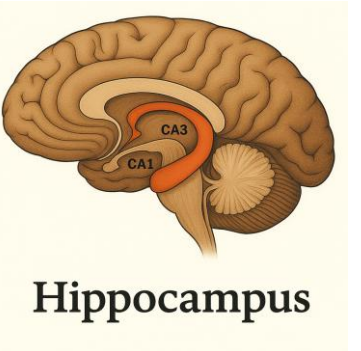
As a result, sensory systems work together in the frontal, parietal, and subcortical parts of the brain, and this co-ordination is essential for cognitive performance. Directly from a biophysical viewpoint, oscillatory dynamics are linked to synaptic plasticity and neuronal transmission, as noted in Petersen, & Posner, (2012).

The Brain's Basis for Memory

The process of memory involves the encoding, storage, and recall of information (Squire, & Zola-Morgan, 1991). From a biophysical standpoint, these mechanisms are founded on synaptic plasticity, electrical conduction via ion channels, and the synchronisation of rhythmic electrical activity in neurons (Bliss, & Lømo, 1973; Fell, & Axmacher, 2011). The hippocampus and other structures in the medial temporal lobe are crucial in the formation of episodic memory and memory consolidation, as noted by Eichenbaum, (2004). The hippocampus's CA1 and CA3 regions are crucial for integrating information in both a contextual and temporal manner (Manns, & Eichenbaum, 2006). The role of the hippocampus and its subregions in memory processes is shown in Figure 2. While the dentate gyrus is involved in differentiating input data and reinterpreting similar events as distinct memory indicators (Leutgeb et al., 2007). The prefrontal cortex, especially the dorsolateral prefrontal area, is engaged in information preservation and revision during working memory (Curtis, & D'Esposito, 2003). The ventromedial prefrontal cortex is responsible for linking long-term memory with working memory (Simons, & Spiers, 2003). The parietal cortex plays a role in attention and conscious awareness

during memory retrieval (Wagner et al., 2005). Information transfer dynamics at the neural network level are revealed by connections between these regions.

Figure 2. The role of the hippocampus and its subregions in memory processes



Source: https://doi.org/10.1016/j.neuron.2004.08.028

At the cellular level, the primary system for memory involves the enhancement of long-term synaptic connections (LTP) resulting from electrical activity (Bliss, & Lømo, 1973). LTP is directly linked to glutamatergic transmission and NMDA receptor calcium permeability, illustrating how ion currents biophysically affect plasticity (Malenka, & Bear, 2004). Furthermore, long-term depression (LTD) contributes to learning and memory loss by diminishing synaptic activity (Bear, & Malenka, 1994). The synaptic plasticity systems provide the biological foundation for the process of learning (Martin, Grimwood, & Morris, 2000). Imaging studies using functional magnetic resonance imaging (fMRI) have shown a significant correlation between the hippocampus and prefrontal cortex during memory encoding (Ranganath et al., 2005). FMRI data suggest that activity in the medial temporal lobe rises during successful memory encoding processes (Davachi, 2006). Studies using electrophysiological data have found that the connection between these two processes is strengthened when theta and gamma

band coordination occurs, further highlighting the significance of oscillatory biophysical systems in memory formation (Lisman, & Jensen, 2013). Hippocampal activity is transferred to neocortical networks during memory consolidation, leading to long-term storage (McGaugh, 2000).

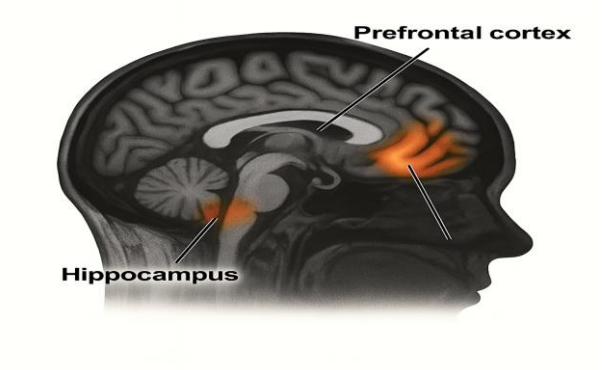
Interaction of Attention and Memory

Awh, Vogel, and Oh, (2006) found that attention and memory function as interdependent systems rather than separate entities. This relationship occurs from a neurobiophysical perspective due to the coordination of rhythmic electrical fluctuations generated by various brain regions (Fries, 2009). Learning efficiency is improved by attention, which decides which information is stored in long-term memory during the process of memory encoding (Chun, & Turk-Browne, 2007). Behavioral studies have demonstrated that carefully processed stimuli result in longer-lasting memory traces (Uncapher, & Rugg, 2009). These studies suggest that attention aids memory consolidation through the regulation of synaptic plasticity at a biophysical level (Martin, Grimwood, & Morris, 2000).

Neuroimaging data using fMRI indicate that the link between the hippocampus and prefrontal cortex becomes stronger during the process of attentional encoding (Ranganath et al., 2005). Figure 3 shows the activation of the hippocampus and prefrontal cortex (fMRI) in relation to attention and memory. Electrophysiology data indicate that this relationship is highly influenced by interactions between theta-gamma wavelengths, with neuronal oscillations

serving as the physical basis for coordinating cognitive processes (Lisman, & Jensen, 2013; Sauseng et al., 2010). Working memory and attention share common neural data, particularly in the prefrontal and parietal areas (Awh, & Jonides, 2001). Attentional focus supports the renewal and maintenance of information by targeting working memory content to specific elements (Gazzaley, & Nobre, 2012). Furthermore, working memory contents also guide the attentional system within the framework of past experiences (Olivers et al., 2011).

Figure 3. Hippocampus and prefrontal cortex activation in the relationship between attention and memory (fMRI)



Source: (Simons & Spiers, 2003; Miller & Cohen, 2001; Eichenbaum, 2017).

From a biophysical standpoint, this interrelationship contributes to the occurrence of coordinated fluctuations in various brain areas (Fries, 2009). The relationship between fluctuations in theta and gamma bands, specifically, enables both the direction of attention and the retention of inputs in sequential memory (Lisman, & Jensen, 2013). This coordination supports the functioning of various neuronal circuits within a unified timing framework, thereby

improving cognitive performance (Sauseng et al., 2010). Attention is key to improving memory encoding, and memory influences the stages of attention and how selective information is processed (Summerfield, & de Lange, 2014). The interrelationship between these elements offers a fundamental framework for a comprehensive understanding of biophysical systems, including synaptic plasticity, neural communication speeds, and recurring fluctuations, as well as cognitive processes (Buzsáki, & Draguhn, 2004; Deco et al., 2008).

Clinical Applications: Attention and Memory Disorders

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder that is marked by episodic memory problems that are related to specific events. In the early stages of the disease, considerable neuronal loss has been observed in the regions of the hippocampus and the medial temporal lobe (Braak, & Braak, 1991). Significant neuronal loss is also observed in these regions (Selkoe, 2002). These losses not only happen at the cellular level but also affect the biophysical dynamics of synaptic plasticity (Palop, & Mucke, 2010), and memory loss is accompanied by impairments in attentional processes, which negatively affect our daily activities (Perry, & Hodges, 1999). Research using functional magnetic resonance imaging (fMRI) has shown that Alzheimer's patients experience hippocampal dysfunction in attention networks, accompanied by decreased connectivity in the prefrontal and parietal cortices (Buckner et al., 2005). The results of electrophysiological tests also showed that the coordination between theta and gamma brain activity was disrupted in patients, which was linked to problems with memory and attention (Stam et al., 2005).

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is typically marked by a person's struggle to maintain attention, excessive impulsive behavior, and heightened levels of activity (Barkley, 1997). This disorder has been shown to involve impairments in both function and structure in the prefrontal cortex and parietal areas (Castellanos, & Proal, 2012). Among the key aspects of cognitive symptoms in attention deficit hyperactivity disorder (ADHD) are reduced working memory capacity and impaired attentional processing skills (Martinussen et al., 2005). Studies using neuroimaging have found that disruptions to the connections between the frontoparietal control network and the default mode network are linked to issues with attention and memory (Cortese et al., 2012). Examination of gamma-band function biophysically reveals a reduction in the frontal regions in ADHD, which complicates focusing one's attention (Clarke et al., 2019).

Schizophrenia

Schizophrenia is a serious psychiatric disorder marked by impairments in attention and working memory (Goldman-Rakic, 1994). Dopaminergic dysfunction in the prefrontal cortex is closely linked to the working memory impairments seen in schizophrenia (Weinberger et al., 2001). Disruptions in connectivity between the parietal cortex and the hippocampus result in impairments of attentional orientation and memory encoding (Meyer-Lindenberg et al., 2005). Studies at the behavioral level have found that patients with schizophrenia struggle with memory tasks that require a lot of attention (Forbes et al., 2009). Research indicates that individuals with schizophrenia experience a decrease in gamma rhythmic electrical oscillations, which leads to problems with coordinating attention and memory functions (Uhlhaas, & Singer, 2010). Studies further suggest that attention and memory play a crucial role not only in fundamental cognitive processes but also in comprehending

neurological and psychiatric conditions (Petersen, & Posner, 2012). Studies of Alzheimer's, ADHD, and schizophrenia have shown that changes in attention and memory connection patterns underlie the clinical manifestations of these conditions (Buckner et al., 2005; Castellanos, & Proal, 2012; Meyer-Lindenberg et al., 2005). From a biophysical standpoint, the decline in rhythmic oscillations, impaired synaptic adaptability, and changes in neural connection patterns observed in these disorders provide the neurophysiological basis for the clinical symptoms reported (Uhlhaas, & Singer, 2010; Palop & Mucke, 2010).

General Clinical Significance

Research indicates that both attention and memory processing, along with core cognitive systems, are crucial for understanding neurological and psychiatric disorders (Petersen, & Posner, 2012). Changes in the connection between attention and memory are a crucial aspect of conditions such as Alzheimer's, ADHD, and schizophrenia, as shown by studies (Buckner et al., 2005; Castellanos, & Proal, 2012; Meyer-Lindenberg et al., 2005).

Future Perspectives

Investigations of attention and memory processes in neuroscience have become increasingly significant, according to Petersen and Posner, (2012). This biophysical approach enables an understanding of these processes not only at the cognitive level but also in conjunction with the electrical and chemical dynamics of neuronal networks (Buzsáki, 2006). Techniques such as functional magnetic resonance imaging (fMRI) and diffusion MRI disclose the network dynamics driving these processes (Sporns, 2011). Combining high-temporal resolution EEG and MEG recordings in biophysical models is crucial for explaining systems of attention and memory processes that rely on repetitive activity (Baillet, 2017).

Future research using multimodal imaging techniques, such as fMRI, EEG, and MEG combined, will produce more reliable results with both temporal and spatial resolution (Baillet, 2017). Developing biophysical network models from complex brain findings enables artificial intelligence and machine learning-based models to offer new clinical opportunities in the early diagnosis of attention and memory disorders (Durstewitz, Koppe, & Meyer-Lindenberg, 2019). Targeting attention and memory networks with neuromodulation techniques, such as TMS and tDCS, offers opportunities for cognitive rehabilitation by physically altering synaptic plasticity (Polanía, Nitsche, & Ruff, 2018). Computer models of biophysics offer a crucial complement to uncovering the network-level consequences of these methods (Deco et al., 2008).

In this context, coordinating neurobiophysical studies with personalized medicine applications will assist in the development of new plans for both cognitive health protection and early disease diagnosis (Insel, 2017). Consequently, a biophysical understanding of memory and attention processes will become a key driver in a broad spectrum of fields, encompassing clinical neuroscience to artificial intelligence-based analyses.

Conclusion

Human cognition is fundamentally based on attention and memory, which are closely linked (Awh, Vogel, & Oh, 2006). Memory encoding and retrieval are facilitated by attention, with prior experiences directing attention as guided by memory (Chun, & Turk-Browne, 2007). The connection between these areas arises from the coordinated activity of various parts of the brain, including the prefrontal cortex, the parietal lobe, and the hippocampus (Miller, & Cohen, 2001). From a biophysical perspective, this interrelationship is predicated on synaptic plasticity mechanisms (LTP, LTD), the synchronisation of neuronal oscillations, and the

swiftness of electrical communication between cortical and subcortical networks (Bliss, & Lømo, 1973; Fries, 2009; Lisman, & Jensen, 2013). Understanding memory and attention processes is crucial for cognitive neuroscience as well as for biophysical modeling and neurophysiological studies (Buzsáki, & Draguhn, 2004; Deco et al., 2008).

Alterations in attention and memory processes are key clinical features in disorders such as Alzheimer's, ADHD, and schizophrenia (Buckner et al., 2005; Castellanos & Proal, 2012; Meyer-Lindenberg et al., 2005). The neurophysiological basis for the biophysical clinical findings seen in these disorders can be attributed to the oscillatory rhythm losses and synaptic transmission disturbances observed (Uhlhaas, & Singer, 2010; Palop, & Mucke, 2010). Advanced imaging techniques, artificial intelligence-aided network analyses, and neuromodulation methods will in the future allow for a more detailed comprehension of attention and memory processes and enable the development of treatment strategies (Durstewitz et al., 2019; Polanía, Nitsche, & Ruff, 2018).Ultimately, understanding the interaction between memory and attention at the biophysical level is crucial across a wide array of disciplines, from cognitive neuroscience to clinical studies. Contributions from this perspective will aid in a comprehensive comprehension of human brain processes (Insel, 2017).

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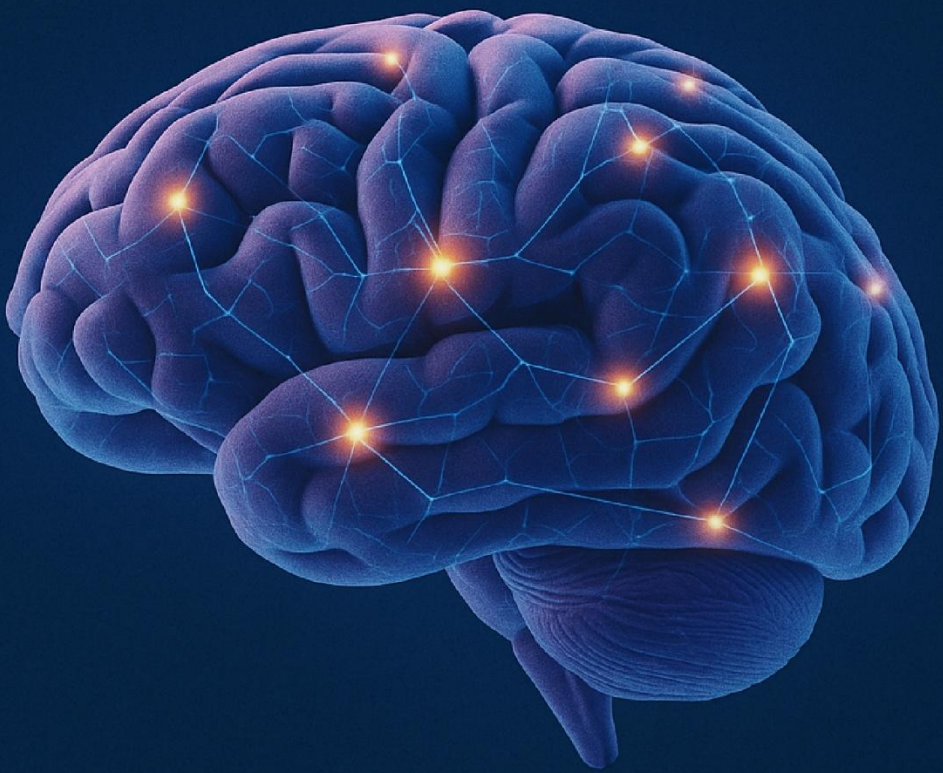

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