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Psychotherapy and Guided Imagery

Intraventricular Angiomatous Meningioma

Highlights

Basic to Advanced Neuropathic Pain

Mystical Experience with Cancer Patients

Discovering Thoughts, Inventing Future

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Mystical Experience with Cancer Patients: Insights from Psychedelic-Assisted Psychotherapy and Guided Imagery

By Jerry B. Brown & Julie M. Brown

Florida International University

Abstract- *Background:* In controlled, clinical studies of the impact of psilocybin on patients with life-threatening cancers, Johns Hopkins and NYU researchers found that the "intensity of the mystical experience" induced by psychedelic-assisted psychotherapy was directly correlated with the alleviation of cancer-related mental distress.

Objective: The purpose of this article is to explore the proposition that the combination of psychotherapeutic guided imagery and psychedelic-assisted psychotherapy could not only alleviate cancer-related psychological distress but also reduce or eliminate physiological tumors.

Methods: The literature surrounding "mystical experience" is discussed; the modalities of psychedelic-assisted psychotherapy and guided imagery psychotherapy with cancer patients are compared; and the anecdotal outcomes of cancer remission among private therapy guided imagery patients are presented.

Keywords: *cancer, mystical experience, neuroimaging, psilocybin, psychedelic-assisted psychotherapy.*

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Result: The following question is proposed for future research: can psychedelic-assisted psychotherapy augmented by guided imagery facilitate the reduction or elimination of tumors in cancer patients?

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"In both trials, the intensity of the mystical experience described by patients correlated to the degree to which their depression and anxiety decreased."

-Johns Hopkins and NYU psilocybin-cancer studies

Introduction

Our contemporary understanding of the common elements in mystical experience is largely based on the ideas of William James (1902), *The Varieties of Religious Experience*, and Walter T. Stace (1961), *Mysticism and Philosophy*. These elements were refined, validated, and incorporated into a 30-question operational definition of mysticism, the Mystical Experience Questionnaire (MEQ30) utilized in the Johns Hopkins studies on the impact of psilocybin on reducing anxiety and depression in patients with life-threatening cancers (Barrett et al. 2015, MacLean et al. 2012).

Author α: Ph.D., is Founding Professor of Anthropology, Global & Sociocultural Studies, Florida International University, Miami, Florida, USA. e-mail: jbbrown@gate.net

Author σ: M.A., LMHC, is a retired integrative psychotherapist who specialized in working with cancer patients.

The five common elements of mystical experience are:

- Unity/Sacredness– deep sense of unity with all of existence; knowledge that "all is one"; profound sense of reverence.
- Positive Mood/Ecstasy– deeply felt sense of well-being; experience of peace and tranquility; irrepressible feelings of joy and amazement.
- Transcendence of Time and Space/Eternity– loss of usual sense of time and space; existing beyond past, present and future; entering a liminal, mythic dimension.
- Authoritative/True Self– authoritative truth value of the experience (noetic); encounter with all-knowing presence; understanding one's authentic self.
- Ineffable/Indescribable– difficulty describing the experience in words; impossibility of adequately communicating it to others.

I. Psychedelic-assisted Psychotherapy

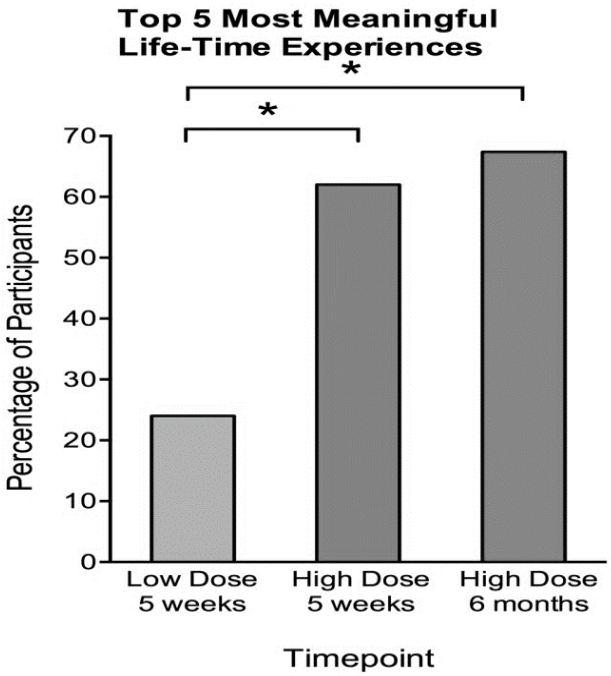
Since 2006 the Johns Hopkins School of Medicine (Johns Hopkins) has been conducting the first research since the 1970s involving the administering of psilocybin to human subjects, including studies of personality changes and of psychedelic therapy for treating tobacco/nicotine addiction and cancer-related distress.

In 2016 Johns Hopkins undertook the largest ever study of psilocybin in treating chronic depression and anxiety among patients with life-threatening cancers. In this randomized, double-blind, cross-over trial, 51 patients were given a low placebo-like dose (1-3 mg/70 kg of body weight) vs. a high dose (22 or 30 mg/70 kg of body weight) in two sessions with six-month follow up. (Griffiths et al. 2016).

In a *Journal of Psychopharmacology* article, Roland R. Griffiths, Matthew W. Johnson, and colleagues report that "High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety" (Griffiths et al. 2016, p. 1). A six-month follow up study showed that these results were sustained in most of the participants.

Some 70 percent of the cancer patients rated the high-dose psilocybin sessions as among the top five

"most meaningful" and "spiritually significant" life experiences. In addition, their post-session mystical experience scores served as statistically significant predictors of therapeutic efficiency in reducing anxiety and depression.



Source: Matthew W. Johnson, Johns Hopkins School of Medicine, "Psilocybin in the treatment of cancer-associated depression and anxiety," Power point presentation, Ottawa, 2018, slide 13.

The daughter of one study participant noted that "This opportunity allowed my dad to have vigor in his last couple of weeks of life – vigor that one would think a dying man could not possibly demonstrate. His experience gave my father peace. His peace gives me strength" (Johnson 2018, slide 16). These outcomes prompted Griffiths to observe that "It's very common for people who have profound mystical-type experiences to report very positive changes in attitudes about themselves, their lives, and their relationships with others." And to exclaim, "To see people who are so beaten down by this illness, and they start actually providing reassurance to the people who love them most, telling them 'it is all okay and there is no need to worry'—when a dying person can provide that type of clarity for their caretakers, even we researchers are left with a sense of wonder" (Schiffman 2016).

a) Guided Imagery-Assisted Psychotherapy

Julie M. Brown, coauthor of this article, is a retired psychotherapist who for twenty-five years specialized in helping cancer patients heal. In her private practice, she worked with a variety of therapeutic modalities, including guided imagery which she studied as a graduate student under her mentor in psycho synthesis.

Guided imagery, also known as visualization, is a technique through which psychotherapists help patients evoke and focus on mental images to facilitate relaxation, healing, and resolution of life issues. In guided imagery-assisted psychotherapy, a person calls on mental images to improve both emotional and physical health (see Samuels, 2003; Epstein, 1989).

This highlights an important distinction between psychedelic-assisted psychotherapy and guided imagery. The Johns Hopkins protocol is *non-directive*, simply encouraging study participants to "trust, let go and be open" and not providing instructions on where to focus. In contrast, the guided imagery modality is *directive*, with the therapist purposefully focusing patients to induce images and assisting in processing and integrating these images.

Often Brown's cancer patients turned to psychotherapy after conventional treatment (chemotherapy, radiation, pharmaceuticals) failed to reduce or eliminate tumors. In the guided imagery sessions, Brown found that patients would at times enter states of mystical experience that empowered both emotional (anxiety, depression) and physical (cancer) self-healing.

b) Guided Imagery Therapy Outcomes

Between 1986 and 2011, Brown worked with 50 cancer patients, the majority of whom achieved full remission as evaluated by oncologists. The profiles and outcomes for three patients are summarized in this table.

Client Profiles and Guided Imagery Therapy Outcomes

	Client #1	Client #2	Client #3
Gender	Male	Male	Female
Profession	Hospital CEO	Physician	Graduate Student
Diagnosis	4th Stage Prostate Cancer	4th Stage Prostate Cancer	3rd Stage Breast Cancer
Psychotherapy Treatment Length	1 Year w/out Conventional Cancer Treatment	2 Years w/out Conventional Cancer Treatment	1 ½ Years w/out Conventional Cancer Treatment
Guided Image	Healing Garden	Spiritual Self	Warrior Self
Main Mystical Experience Elements	Unity-Oneness, Positive Mood	Unity-Oneness, Authentic Self	> Time/Space, Positive Mood
Outcomes	Anxiety Reduced, Full Remission > 5 Years	Anxiety Reduced, Full Remission > 7 Years	Anxiety Reduced, Full Remission > 5 Years

Source: Julie M. Brown, LMHC, Select Client Profiles, 1986-2011

Depending on the client's situation, Brown frequently combined guided imagery in the context of psychotherapy with a complementary cancer approach. A complementary cancer approach may integrate a variety of tools including, but not limited to, emotional release work, breath work, nutrition, exercise, and meditation. This approach can help reduce the side effects of conventional treatment, improve client emotional and physical well-being, and enhance the healing process.

Unlike the controlled Johns Hopkins study involving 51 participants, Brown's 50 case studies were neither validated by independent observers nor subjected to methodological controls – except for the patients' cancer status which was monitored by their oncologists. Nevertheless, the seminal role of mystical experience in both psychedelic-assisted psychotherapy and guided imagery psychotherapy raises important questions.

c) Guided Imagery Questions for Future Research

In the case of Brown's guided imagery outcomes with cancer patients, significant questions are:

- *Can success in healing cancer utilizing guided imagery be replicated and validated?* Beyond Brown's anecdotal cancer outcomes have other therapists been able to reduce or eliminate tumors utilizing guided imagery? Could healing have taken place in this context without a complementary cancer approach, or was it the combination of this approach and guided imagery that facilitated remission?
- Can psychedelic therapy protocols be integrated into guided imagery therapy?

As a psychotherapist and a person with significant personal psychedelic experience, Brown hypothesizes that the ability to administer psilocybin to psychotherapy patients could conceivably shorten the healing process, possibly from years to months. Given that clinical trials on psilocybin for addressing major depression disorder have been granted "breakthrough therapy" designation by the U.S. Food and Drug Administration, what changes in state and federal policies, and in professional regulations, would have to take place so that psychiatrists and psychotherapists could legally integrate psychedelics into conventional treatment modalities?

d) Psychedelic Therapy Questions for Future Research

In the case of Johns Hopkins psychedelic therapy outcomes with cancer patients, significant questions are:

- Can psychedelic-assisted psychotherapy be used not only to alleviate psychological anxiety and depression in patients with life-threatening cancers, but also to facilitate physiological healing among cancer patients?

Given the pivotal role of mystical experience in both *short-term* psychedelic-assisted psychotherapy and *long-term* guided imagery psychotherapy, could psychedelic therapy combined with guided imagery possibly reduce or eliminate tumors in late-stage cancer patients?

- Will long-term, costly psychotherapy eventually be replaced by short-term, more affordable psychedelic-assisted psychotherapy?

Since short-term psychedelic therapy has achieved positive and sustained outcomes in 70 percent of the participants, based on one or two high-dose psilocybin sessions administered over several weeks, will it eventually replace, or significantly enhance, long-term psychiatric and psychotherapeutic modalities which require years of treatment and cost thousands of dollars?

II. Mystical Experience and Healing

It is well-established that mystical experiences have historically played a pivotal role in indigenous shamanism and world religions, such as the miracles

surrounding Moses' burning bush and Jesus' baptism (Brown and Brown, 2019; Brown and Brown, 2016; Winkelman, 2019). What is less well-known and quite unexpected is the discovery that mystical experiences are the catalyst for healing in contemporary psychedelic research.

Two studies of the impact of psilocybin on cancer patients, conducted at Johns Hopkins and NYU, found that "In both trials, the intensity of the mystical experience described by patients correlated with the degree to which their depression and anxiety decreased" (Hoffman 2016).

In other words, research scientists have reliably occasioned mystical experiences – "flights of the soul" traditionally thought to be beyond the scope of empirical science – in clinical settings by administering high-dose psilocybin. Furthermore, it turns out that these experiences hold the key to positive patient outcomes in psychedelic-assisted psychotherapy. Let this enigma sink in for a moment.

a) Three Seminal Studies

In the 1960s urban legends began circulating, claiming that psychedelics could allow intrepid trippers to meet spirit guides, to travel to other dimensions, and even to know God. In fact, the new science of psychedelics was in part inspired by the initiatory mystical experiences of early psychonauts: Stanislav Grof's cosmic consciousness revelations on LSD in Prague (1993, pp. 15-16); Michael Harner's near death journey on ayahuasca in the Amazon (1990, pp. 3-5); and Timothy Leary's mind-expanding awakening on psilocybin mushrooms in Cuernavaca, Mexico (1960, pp. 11-34), to name but a few. Over time, the ability of psychedelics to generate authentic mystical experiences was confirmed by three seminal studies.

The first, the Miracle of Marsh Chapel (also called the "Good Friday Experiment") was a psychedelic research experiment carried out by Walter N. Pahnke under the auspices of Leary's Harvard Psilocybin Project. On Good Friday 1962, Pahnke randomly divided twenty volunteer Protestant divinity students into two groups assembled in a small room in the basement of Marsh Chapel on the campus of Boston University. In this controlled double-blind study, half the students received capsules containing thirty milligrams of psilocybin and the other half received a large dose of niacin (vitamin B3) as a placebo. The results were compelling. Almost all members of the group receiving psilocybin reported profound mystical experiences.

As Pahnke reports, "The persons who received psilocybin experienced to a greater extent than did the controls the phenomena described by our typology of mysticism" (Doblin 2012, p. 85). He built a follow-up survey into the research design, which found that six months after the experiment the psilocybin subjects reported persistent positive, and virtually no negative changes in their attitude and behavior.

The second study showed that the Good Friday Experiment could withstand the test of time and scrutiny by independent reviewers. A 25-year follow-up investigation conducted in 1987 by then-graduate student Rick Doblin, founder of the Multidisciplinary Association for Psychedelic Studies (MAPS), documented that "all seven psilocybin subjects participating in the long-term follow-up, but none of the controls, still considered their original experience to have had genuinely mystical elements and to have made a valuable contribution to their personal lives." Doblin (2012, p. 87) concluded that Pahnke's research on synthetic psilocybin "cast considerable doubt on the assertion that mystical experiences catalyzed by drugs are in any way inferior to nondrug mystical experiences."

In assessing Pahnke's research, Walter H. Clark, recipient of the American Psychological Association's Award for contributions to the psychology of religion, states "There are no experiments known to me in the history of the scientific study of religion better designed or clearer in their conclusion than this one" (Doblin 2012, pp. 87-88).

A third round of studies, initiated more than 40 years after the Good Friday Experiment, was conducted at Johns Hopkins School of Medicine. In two papers, Griffiths and his colleagues empirically demonstrated that psilocybin could regularly result in mystical experiences with lasting benefits for participants (Griffiths et al. 2008; Griffiths et al. 2006). These double-blind studies found that: psilocybin was safe in structured, clinical settings; generated one of the five most meaningful life experiences for most participants; and produced improvements in mood and quality of life that were still present 14 months after the sessions.

b) How Does Mystical Experience Facilitate Healing?

The rigorous psychedelic therapy studies of stress reduction and the anecdotal guided imagery therapy cases of cancer remission described above suggest that mystical experience can facilitate both mental and physical healing. "How" this healing takes place is the theoretical Holy Grail of psychedelic-assisted psychotherapy.

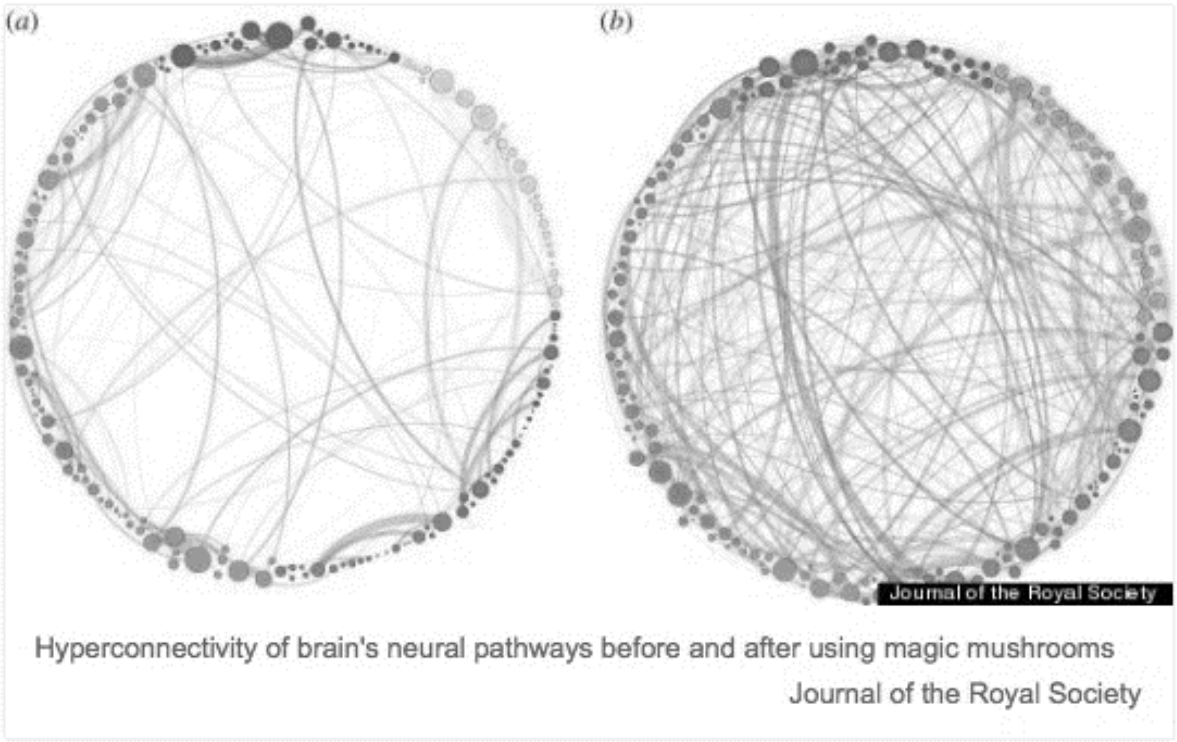
Our quest to unravel this mystery begins with the insights of three mind explorers: Roland R. Griffiths, grandfather of the psychedelic renaissance; Robin Carhart-Harris, pioneer of psychedelic brain neuroimaging; and Carl G. Jung, who with Sigmund Freud laid the foundations of modern psychotherapy.

In essence, Griffiths observes that "the psilocybin experience enables a sense of deeper meaning, and an understanding that in the largest frame everything is fine and that there is nothing to be fearful of" (Schiffman 2016). How the brain expands from

ordinary consciousness to encompass this "largest frame" is visually revealed in Carhart-Harris's functional magnetic resonance imaging (fMRI) of the brain's neural pathways before and after ingesting psilocybin mushrooms.

III. Brain's Neural Pathways

Before and after Magic Mushrooms



Source: G. Petri, P. Expert, et al., Homological scaffolds of brain functional networks, Journal of the Royal Society, December 2014, p. 8.

Psychedelics allow us to leave the brain's "default-mode network" (Carhart-Harris et al. 2014), the brain's everyday information highway, and travel into areas of the mind accessible in non-ordinary states of consciousness, thereby creating a "superhighway to the unconscious" and access to mystical experience. In summarizing the findings of neuroimaging research with psychedelic drugs, Carhart-Harris (2014, p. 18) concludes, "Indeed, psychedelics greatest value may be as a remedy for ignorance of the unconscious mind."

IV. Inner Self-healing Intelligence

It is Jung's (2017) "spiritual self" that embodies insights that emerge from the unconscious mind. Beyond Freud's model, Jung proposes the existence of a "spiritual self," also called "spiritual consciousness." Through dreams, messages from the spiritual self are brought into awareness.

Mystical experiences arise when the doors of perception are flung wide open so that the spiritual self can surface from the depths of the psyche, empowering us to heal and understand that in the cosmic scheme of things "all is well." As one of the pioneers of psychedelic psychotherapy, Stanislav Grof has guided over 3,000 LSD sessions. Based on his unparalleled experience with LSD and encyclopedic knowledge of the psychedelic literature, Grof (2019) observes that "Entering these [holotropic, transpersonal, mystical] states activates an inner self-healing intelligence, which automatically guides the process to unconscious material that has a strong emotional charge and is close to the threshold of consciousness. It then spontaneously brings this material to the surface for processing."

In this context, it is worth noting that Grof has documented significant instances of auto-punitive emotions correlated with the emergence of cancer. In *The Human Encounter with Death,* he reported on research in which high dose LSD (200 to 600 micrograms) was given to terminally ill cancer patients (Grof and Halifax, 1977). In this study, Grof and associates at the Spring Grove State Hospital in Baltimore "…saw surprisingly frequent instances of severe guilt, feelings of self hatred, and autopunitive tendencies that had preceded the clinical manifestation of cancer by years or decades." They also found that "It was not infrequent that cancer patients in their LSD

sessions saw direct links between such tendencies within themselves and their malignancies."

a) Can Positive Emotions Impact Immune Response?

To investigate the above findings from a medical perspective, it is essential to seek empirical evidence on the impact of mental states on healing cancer. It is important to go beyond the psychological phenomena of "mystical experience" and "inner self-healing intelligence" to determine if there is physiological evidence that positive emotions, such as those engendered by mystical experience, can significantly activate the body's immune system.

Research conducted at the Faculty of Medicine at the Technion in Israel suggests that the *prima facie* answer to this question is "yes." Studies of mouse models involving melanoma and lung cancer found that activation of the brain's reward system helps regulate immune system function and enhances immune response (Ben-Shaanan, et. al. 2018). Specifically, activation of the dopamine-releasing neurons in the ventral tegmental area (VTA) of the brain significantly impacted tumors, resulting in a 46.5 percent reduction of tumor size after 14 days.

V. Conclusions

This paper shows that, in addition to appearing in dreams, the spiritual self may emerge through mystical experiences occasioned by psychedelic-assisted psychotherapy or evoked by guided imagery therapy. While controlled, clinical studies (n=51) at Johns Hopkins School of Medicine found that psychedelic-assisted psychotherapy alleviates anxiety, depression, and fear of death among patients with life-threatening cancers, anecdotal observations (n=50) among cancer patients being treated in private practice found that guided imagery psychotherapy reduces or eliminates tumors among advanced stage cancer patients. Based on these observations, the following question is proposed for future research: can psychedelic-assisted psychotherapy augmented by guided imagery facilitate the reduction or elimination of tumors in cancer patients?

Hopefully, these reflections on the role of mystical experience in psychotherapy will inspire further exploration of this unique phenomena that holds a key to healing and well-being.

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Conflict of interest

The coauthors have no conflicts of interest neither in writing this article nor regarding the subject matter of this article.

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Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease

By Vic Shao-Chih Chiang

University College London

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Neuroinflammation Interactions with Mitochondria: Implications for Alzheimer's Disease

Neuroinflammation affects Mitochondrial Function

Vic Shao-Chih Chiang

Abstract- The mitochondria are the powerhouses of the body, which is paramount for the central nervous system given their high energy expenditure. This high dependence on the mitochondria renders mitochondrial dysfunctions to impair the central nervous system, as seen in neurodegenerative diseases. This article concentrates on the neurodgenerative disease, Alzheimer's disease and the well-established neuroinflammation pathophysiology, from a mitochondrial perspective. I first focused on the energy production functions of the mitochondria, and the mitochondrial DNA, imperative for mitochondrial function. For instance in their aberrations in Alzheimer's disease, and *in vitro* experiments with inflammatory markers that drove damages to the mitochondria DNA. Subsequently, I discussed about mitochondrial biogenesis using expression studies with correlated changes in Alzheimer's disease and stem cells whereby mitochondria are critical regulators of their fate, pertinent to Alzheimer's disease. Finally, I accentuated on emerging technologies that enable disentangling the abstruse nature of mitochondria, and some uprising areas of mitochondria research deserving attention from the lens of Alzheimer's disease. Overall, there is a plausible link between Alzheimer's disease, neuroinflammation, and mitochondrial mechanisms, but current studies are limited to causally address this question. I presented several improvements and strategies that could be taken to advance the understanding of this relationship in future studies.

I. Introduction

Mitochondria are 0.5 – 1.0 μm cellular organelles that generate energy in the form of ATP [1]. By virtue of the high energy expenditure in the central nervous system, mitochondria pose exceptionally important roles[2]. Corresponding to their gravity, multiple neurodegenerative diseases exhibit mitochondrial dysfunction[3–5]. Alongside mitochondrial dysfunction, neurodegenerative diseases frequently accompany chronic inflammation within the brain[6–8]. Scholars termed this as "neuroinflammation" [9] and while this phenomenon serves a diverse range of purposes, it most fundamentally associates with the body's natural innate immune response to eliminate unwanted material and initiate repair[10]. Is there a relationship between neuroinflammation and mitochondrial function? Could neuroinflammation be the cause of mitochondrial dysfunction? To answer this, this article concentrates on sporadic Alzheimer's disease (AD) due to decades of research since the 1970s that supports a role of inflammation in AD pathophysiology [11–14]. AD is a disease that leads to progressive synaptic degeneration and neuronal death with ageing[15]. In the US, researchers estimated the prevalence of AD to affect one in three elderlies [16] and ascribed to a financial burden estimated to be well over $200 billion [17]. This article aims to answer whether neuroinflammation may affect mitochondrial function in the context of AD in relation to three fundamental aspects of mitochondrial function: mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis.

II. Neuroinflammation may affect Mitochondrial Energy Production

Mitochondria is the critical site of energy production through the tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS) during respiration[18]. In particular, OXPHOS generates a large amount of energy in the form of ATP by electron transfer from NADH and FADH2 in the electron transport chain[18]. Respiration and OXPHOS energy production are disrupted in AD (Table 2). Ageing studies were included in Table 2 to provide further insights since ageing is the greatest risk factor for neurodegeneration[19]. From this, OXPHOS and respiration appear to reduce with AD and ageing. In saying that, these studies deployed animal models, which deviates from human AD progression, ergo, researchers should attend to possible caveats of clinical translatability[20]. Aside from the differences reported, some of these animal studies have also provided results for other components of the electron transport chain. However, these failed to demonstrate any differences compared to the control. The failure of global changes in these components can create a selection bias where researchers make interpretations only on the OXPHOS components they selected to measure. Respiration is an objective measure for energy production. Therefore, future studies should include

Corresponding Author: UCL Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, UK.
e-mail: vic.chiang.15@alumni.ucl.ac.uk

incorporating respiration as the primary outcome to reduce ambiguity in interpretation. Researchers can then further investigate these differences in respiration which specific components of the electron transport chain may drive this. Two reviews have summarized older studies that have consistently demonstrated that inflammatory cues affected respiration[21,22]. One study focused on how NO inhibits respiration in neurons due to NO restriction of complex I[21]. Another review concentrated on sepsis, which is the acute systemic inflammation from exposure to bacterial endotoxins (e.g., lipopolysaccharide LPS)[22]. It summarizes clinical, animal, and cellular studies and provides countenance to the view for reduced respiration, ATP/ADP ratio, and protein expression of OXPHOS complexes during sepsis[22]. Two other studies not covered in these reviews tendered supplementary support that inflammation does affect measurements relevant to mitochondrial energy production. The LPS treatment of murine macrophages (B6-MCL) and bone marrow-derived macrophages resulted in the complex IV gene and protein expression increase[23]. In tandem with this, another study espoused this relationship in the context of feeding different lipid-based diets to overweight subjects[24]. The comparing diets developed differences in pro-inflammatory proteins in the plasma, including IL1β, macrophage inflammatory protein 1α, and serum amyloid P [24]. Surprisingly, with the decrease in plasma inflammatory proteins, their microarray data showed down-regulation of various OXPHOS-related genes in the peripheral blood mononuclear cells of these subjects [24]. These studies present evidence that inflammation may affect mitochondrial energy production. Notwithstanding, their results displayed opposing views regarding how it perturbed mitochondrial energy production. On the grounds that these researchers did not undertake further experiments to disentangle the mechanisms for these observations, it is imperative to enunciate a more solid framework to construe the data. For example, reduced energy production may not always be inimical, such that it may reduce the amount of oxidative stress [24]. It would be context-dependent whether changes in mitochondrial energy production are deduced as beneficial or adverse. Likewise to the abovementioned, future studies should consider respiration as the primary outcome to reduce the indefiniteness of any speculations. In addition to that, by virtues of cell and tissue-specificity most probable for the effects of inflammation on mitochondrial energy production, future research in this domain specific for AD is warranted. Neuroinflammation likely affects mitochondrial energy production, but its existence in circumstances of neurodegeneration awaits discovery.

III. Neuroinflammation may affect Mitochondrial DNA

Mitochondria possess DNA (mtDNA), and unlike nuclear DNA, it transcribes and replicates outside of the cell cycle[25]. Due to the mtDNA encoding for pivotal proteins for the mitochondria, any adverse changes to this DNA may subsequently develop the impaired mitochondrial function[25]. AD unerringly leads to changes in the mtDNA content and increases the number of mutations (Table 2). Single mitochondrion may contain multiple mtDNA, and single cells contain multiple mitochondria. The multiple mtDNA and mitochondria put the cells at risk of heteroplasmy, which refers to the presence of heterogeneous mtDNA within the same cell[26]. Mutations present in heterogeneous mtDNA may gain power through clonal expansion that can occur rapidly independent of the cell cycle [26]. Accumulation of adverse mtDNA mutations may compromise mitochondrial functions. Further to this, mtDNA changes appear to be site-specific [27], henceforth future studies should demarcate the most vulnerable sites to determine therapeutic priorities. Only a paucity of studies exists which examines how inflammation may directly affect mtDNA. Researchers identified using TNFα and IL1β treatments in primary human chondrocytes to increase mtDNA breaks [28]. Germane to this alludes to a study utilizing primary murine peritoneal macrophages [29]. They observed LPS translocating mtDNA into the cytoplasm through unknown interactions with the cryopyrin inflammasome [29]. The authors speculated this as adverse on the grounds that the loss of mtDNA from the mitochondria could debilitate mitochondrial function[29]. These limited data are adjuvant to the notion that inflammation may affect mtDNA. However, substantially more studies are required to ascertain this effect, especially those relevant to the central nervous system. Major drawbacks with these studies lie in their insufficient exploration of the mtDNA. For example, future studies should recognize the importance of identifying heteroplasmy and specific types of mtDNA breaks or mutations that ensue with inflammation. MtDNA demonstrated the possibility to be affected by neuroinflammation, but whether this is present in the central nervous system remains to be explored.

IV. Neuroinflammation may affect Mitochondrial Biogenesis

Mitochondria are constantly undergoing turnover to replace damaged mitochondria with functional counterparts [18]. The process of generating new mitochondria is termed "mitochondrial biogenesis" 18. Disruptions to this process may affect the number of mitochondria available to carry out paramount cellular functions. The homeostasis of mitochondrial biogenesis

appeared to be disturbed in AD (Table 3), evident in the overall reduction of gene and protein expression related to mitochondrial biogenesis. However, this trend contrasts with this study[30], where researchers found mitochondrial biogenesis to increase in AD. This study experimented with primary hippocampal neurons derived from the Tg2576 AD mice model in comparison to those that originated from wild-type mice[30]. They further subjected these neurons to oxidative stress to exacerbating neurodegeneration[30]. Based on their bromodeoxyuridine labelling, they unearthed an increase in mitochondrial biogenesis[30]. Their explanation for this contingent finding was the mtDNA of these neurons had a reduced half-life, which reciprocally stimulated additional mitochondrial biogenesis [30]. From this, I hypothesize that impairments in mtDNA may precede dysfunctional mitochondrial biogenesis. The initial compensation to counteract detrimental effects from impaired mtDNA through intensifying mitochondrial biogenesis may also become dysfunctional at later stages of AD. Could neuroinflammation affect mitochondrial biogenesis? We can take clues from hypoxia studies as NO is generated[31]. Mice subjected to hypoxia had increased gene expression of PGC1α, NRF1, and TFAM within their brains[31]. Additionally, with the observed strengthening of mitochondrial density in their brains, researchers inferred that mitochondrial biogenesis augmented[31]. This effect was known to be directed by NO since changes in mitochondrial biogenesis were absent in neuronal and endothelial NO synthase gene-deficient mice[31]. Other studies of the central nervous system detected simultaneous changes in inflammation and mitochondrial biogenesis (↑ plasma chemokine ligand 11 protein, ↑ PGC1α protein[32]; ↓brain NFκB, chemokine ligand 11 genes, ↑ PGC1α, NRF1, TFAM[33]). However, the researchers did not further correlate these variables in these studies. Several other studies likewise support the notion that inflammation affects mitochondrial biogenesis, albeit not in the central nervous system. A good illustration exemplifies in a study that treated human cardiac AC16 cells with TNFα[34]. This experiment resulted in the down-regulation of PGC1α protein expression[34]. Furthermore, LPS treatment of human gingival fibroblasts diminished protein expressions of PGC1α and TFAM[35]. Another example was the human knee chondrocyte study carried out by [36] that found IL1β treatment to reduce protein levels of PGC1α, TFAM, NRF1, and NRF2. From these studies, it can be asserted that neuroinflammation affects mitochondrial biogenesis. However, it remains equivocal whether mitochondrial biogenesis is increased or decreased with inflammation. It is imperative to consider the inflammatory mediators utilised in these studies as their effects on mitochondrial biogenesis may be distinct from each other. Neuroinflammation involves a plethora of inflammatory mediators, and therefore, the synergistic or antagonistic effects on mitochondrial biogenesis from different combinations require to be elucidated. In vivo AD studies of chronic inflammation are similarly sine qua non to address the drawbacks of existing studies on inflammation and mitochondrial biogenesis. Neuroinflammation affects mitochondrial biogenesis, but elaborate substantiation in in vivo AD studies awaits.

V. Neuroinflammation and Mitochondria in the Context of Stem Cells

Memory is impaired in AD patients, which correlates with hippocampal degeneration, a site imperative for adult neurogenesis (reviewed in [37]). Supporting clinical evidence espouse abated neurogenesis in AD patients (reviewed in [37]). In several rodent studies, amelioration of the AD sequalae oftentimes accompanies rescued neurogenesis (reviewed in [37]). For example, in an immunotherapy study, the successful delivery of antibody therapeutics across the blood-brain barrier promoted hippocampal neurogenesis[38]. Another study enabling better causal inference, directly administered mesenchymal stem cells, which can differentiate into neuronal-like cells, demonstrated reversal of aberrant signalling pathways related to AD *in vitro* [39] and in 3x Tg-AD mice model [40]. Given that the mitochondria are key signalling organelles for stem cell fate (reviewed in [41]), it is highly plausible that the observed changes in AD symptomatology may mediate through the mitochondria. For instance, stem cell fates may be controlled through the mitochondria by generating reactive oxygenspecies (ROS), influencing bioenergetics, as well as mitochondrial dynamics (reviewed in [41]). Particularly relevant to AD are neural stem cells and ample evidence likewise buttress mitochondrial regulation through affecting their proliferation, daughter cells, and transcriptional changes especially through mitochondria metabolism (reviewed in [42]). Several of the mitochondrial components involved have been mentioned above to be altered by neuroinflammation. For instance, ROS increases neural stem cell self-renewal [43] and with correlative evidence, scholars have postulated NLRP3 inflammasome to modify mitochondrial ROS production [44]. Mitofusin-2 is a pivotal component in mitochondrial dynamics, and essential for the differentiation of induced pluripotent stem cells into cortical neurons [45]. Recently, transgenic mice overexpressing mitofusin-2 demonstrated its critical roles in response to LPS-induced neuroinflammation [46]. In essence, I hypothesize the mitochondria to mediate the effects of stem cell changes in AD through neuroinflammation mechanisms, which require vindication with mechanistic *in vivo* studies.

VI. Technology to Study Neuroinflammation effects on Mitochondria

In order to rigorously obtain scientifically valid data to answer the plethora of experimental questions described throughout this review, the methodology deployed is the perforce consideration factor. Methods for studying the mitochondria has advanced dramatically over the past few decades from studying their morphology and metabolism to their physical properties. First, the three-dimensional ultrastructure of the mitochondria requires resolution through electron microscopy (reviewed in[47]). However, traditional methods of manual segmentation of mitochondria imaging in electron micrographs become rate-limiting in the contemporary data-driven era (reviewed in[47]). Therefore a recent study utilized machine learning in the form of a recurrent neural network to enable automated detection and segmentation of the electron micrographed mitochondria[47]. To conduct analysis beyond visualization, isolating the mitochondria is a pivotal method for detailed molecular examination. Several methods exist for this purpose that has varying success with regards to the number of mitochondria retained and preservation of membrane integrity (reviewed in[48]). One study compared between three different methods, and ferreted out there was no superiority of one method, but each method harboured different strengths, either having a higher yield of mitochondrial protein and mtDNA copy numbers, higher activity retained in the isolated mitochondria or better membrane integrity[48]. Ergo, researchers were recommended to carefully assess which methods most suit them depending on the purpose of their research. As mentioned previously, mitochondrial ROS has tremendous implications in Alzheimer's disease. There have been endeavours of measuring mitochondrial ROS using redox-active probes, but these were limited due to the probe oxidation by several ROS (reviewed in [49]). One study implemented an electron paramagnetic resonance approach that enabled overcoming this hurdle to identify specific ROS generated[49]. Another challenge with ROS is their short lifetimes and high reactivity (reviewed in[50]).One recent solution employed relaxometry from field magnetometry achieved quantum sensing of ROS at the mitochondrial resolution[50]. A myriad of methods is commensurately materializing to understand the physics associated with mitochondria. To name a few, an emission probe was developed to monitor mitochondrial viscosity, cardinal for understanding damaged mitochondria[51], as well as a molecular thermometer to measure the temperature in mitochondria, which impart information on cellular inflammation[52]. Above all, we are at a time where exciting avenues of mitochondria research could be sought through the advancements in vanguard methods to dissect the wonders of the mitochondria.

VII. Future Directions

Beyond the AD topics discussed in the review in the context of mitochondria and neuroinflammation, a myriad of emanating areas of the mitochondria require to be unearthed for their potential in AD pathophysiology. For example, the TCA cycle in the mitochondria generate metabolites for epigenetic mechanisms, yet it was only recently discovered the exigent impact of mitochondria on epigenetics (reviewed in[53]). Epigenetics is similarly infiltrated in AD pathophysiology in the realm of DNA methylation, histone modifications and non-coding RNAs (reviewed in[54]). Another area that is beginning to recognize mitochondria as new players is firing rate homeostasis that stabilizes neural circuit function by maintaining firing rate distribution among neurons[55]. The authors laid out cogent arguments for the mitochondria as part of this homeostatic machinery using robust theoretical frameworks[55]. Vis-à-vis AD, indeed several studies endorsed the claim of an impaired firing homeostatic control in AD. These studies were conglomerated in two articles led by Inna Slutsky whereby a dysregulated integrated homeostatic network may drive causations in AD progression at its early stages (reviewed in[56]; reviewed in[57]). The final uprising area in mitochondria research I want to accentuate is gut microbiota. In one study through trans-kingdom network analysis, mitochondria in the liver exhibited improved metabolism through metabolites derived from the *Lactobacillus* genus[58]. Another study leveraged blood and faecal samples found correlations between mitochondria-related inflammation with the *Lachnospiraceae* family, amongst other findings[59]. This intersects with the role of gut microbiota in AD pathogenesis, that have already garnered a gargantuan amount of attention in the past decade (reviewed[60]). There are an abound of approaches that strive to implement these insights into AD treatments such as using faecal microbial transplants (reviewed in[60]). In saying that, the efficacy and safety of these treatments remain to be conclusively grasped, and understanding the role of mitochondria in their effects is crucial for this endeavour. As can be seen, a variety of novel areas in mitochondria research are being developed. The intersection of these areas of epigenetics, firing rate homeostasis, and gut microbiota with AD, indicate ripeness of exploring these in the crossover between AD, neuroinflammation, and mitochondria.

VIII. Conclusion

Sporadic Alzheimer's disease is under a chronic state of neuroinflammation. Simultaneously, AD patients exhibit signs of mitochondrial dysfunction. Their

mitochondria have a reduced capacity to carry out energy production. In addition, increased mutations in their mitochondrial DNA could impair the transcription of components for mitochondrial function. These are in conjunction with disturbed homeostasis of molecular components required for mitochondrial biogenesis. Altogether, these may be culprits for altered stem cell fates that goads AD pathophysiology. This article answers whether the neuroinflammation in AD may be responsible for the observed mitochondrial dysfunction. However, I raised more questions than answers due to the limited amount of data available and the substantial amount of research still required. Although limited, existing data supports neuroinflammation to affect mitochondrial energy production, mitochondrial DNA, and mitochondrial biogenesis. To answer this question conclusively, we need future in vivo central nervous system studies in the context of AD, using the emerging technologies I described. These studies should generate primary outcomes that minimize the possibility of any ambiguity in interpretation. Other measurements taken must spread in breadth and depth to correspond to mitochondrial dysfunction data in AD patients. In tandem with these, researchers must account for the complexity of neuroinflammation demands in their experimental design, and emphasize the potential of emerging areas in epigenetics, firing rate homeostasis, and gut microbiota. AD is a highly prevalent disease that contributes to an immense societal burden. Understanding how the underlying neuroinflammation contributes to AD could help develop novel or improved strategies to combat this.

Conflict of interest

The author declares no conflict of interest.

Table 1: Changes in mitochondrial OXPHOS and respiration in Alzheimer's disease and ageing

Study Sample	Sample Type	Changes in OXPHOS / respiration (methodology of assessment)	Reference
Male Wistar Rats (20 months)	Hippocampus	□ ↓ state 3 respiration (initiated with ADP) (Clark electrode) □ ↓ Complex I & IV activity (spectrophotometry)	61
Female triple transgenic AD mice (3xTg-AD) (3 months)	Hippocampus	□ ↓ mitochondrial respiration (Clark electrode) □ ↓ mitochondrial respiration (Seahorse XF-24 metabolic flux)	62
Male Wistar rats (30 months)	Cortex	□ ↓ATP synthase (1D-SDS gel) □ ↓ Complex I (1D BN-gel & 2D SDS-gel)	63
Male Wistar rats (24 months)	Brain	□ ↓ Complex I activity (mitochondrial particles)	64
APPswe/PS1dE9 mice (3 months)	Hippocampus	□ ↓ state 3 respiration (initiated with ADP) (Clark electrode) □ ↓ Complex I, II, III, IV (Western blotting)	65
Female Wistar rats (24 months)	Hippocampus, cortex, cerebellum, brainstem	□ ↓ Complex I, II, III, IV activity (spectrophotometry)	66
NMRI-mice (24 months)	Frontal brain region	□ ↓ Complex I, II, IV activity (respirometer) □ ↓ ATP levels (bioluminescence)	67

Table 2: Changes in mitochondrial DNA in Alzheimer's disease and ageing

Study Sample	Sample Type	Changes in mitochondrial DNA (methodology of assessment)	References
AD patients (76.3 yrs)	Hippocampal pyramidal neurons	□ ↑total mtDNA deletions (qPCR N4:N1) □ ↑ size & ↑ number of mtDNA deletion break points (long extension PCR) □ ↑ "common" & "major arc" mtDNA deletions (Sequencing) □ ↑ single nucleotide variants (Sequencing)	68
Caucasian male (67 - 89 yrs)	Putamen	□ ↑ m.3243A>G tRNA mutation (Sequencing) □ ↑ clonal ~50bp deletions in the control region (Sequencing)	69
Male Fischer 344 rats (26 months old)	Frontal cortex	□ 25% ↓ in mtDNA content (qPCR D-loop: β-actin) □ 37% ↑ in 4.8kb deletions (qPCR 4.8kb deleted region: D-loop)	70
AD patients (56 - 86 yrs)	Different brain sections	□ ↑ mtDNA deletion in cerebellar granule cells > pyramidal cells (qPCR N4:N1)	27
AD patients (59 - 93 yrs)	Frontal cortex	□ ↓ mtDNA content (qPCR ND2: 18S rRNA) □ ↑ heteroplasmy (Sequencing) □ ↑ T414G mutation (PNA-clamping PCR)	71
AD patients (65 - 90 yrs)	Blood	□ ↑ heteroplasmy (sequencing & PCR)	72

qPCR, quantitative real-time polymerase chain reaction

Table 3: Changes in mitochondrial biogenesis in Alzheimer's disease and ageing.

Study sample	Sample type	Changes in mitochondrial biogenesis	Method of assessment	Reference
Male Fischer 344 rats (24 - 28 months)	Livers	↓ nuclear Nrf2 protein expression	Western blotting	73
AD patients	Hippocampus	↓ PGC1α gene expression	Microarray & qPCR	74
Female Wistar rats (24 months)	heart, lung, liver	↓ intracellular NAD+ & NAD;NADH ratio (sirtuin 1 substrate – regulates PGC1α)	Thiazolyl blue microcyclcing assay	75
AD Mice model (Tg2576 line)	Primary hippocampal neurons (treated with rotenone & H_2O_2)	↑ mitochondrial biogenesis	BrdU labeling	30
AD patients (65 - 91 yrs)	Hippocampus	↓ protein expression of PGC1α, NRF1/2 & TFAM	Western blotting	76
AD Mice model (APPswe/PS1dE9)	Brain	↓ PGC1α gene expression	qPCR	65

Bromodeoxyuridine, BrdU; mitochondrial transcription factor A, TFAM; nicotinamide adenine dinucleotide, NAD; nuclear respiratory factor, NRF; peroxisome proliferated-activated receptor gamma co-activator one alpha, PGC1α; quantitative real-time polymerase chain reaction, qPCR

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Rare Case of Young Patient with Intraventricular Angiomatous Meningioma

By Gabriel Carvalho Heemann, Vinicius Rosa de Castro, Normando Guedes Pereira Neto, Camila Bocchi, Otavio Garcia Martins, Rafael Silva Paglioli & Ricardo Chmelnistky Wainberg

Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul

Abstract- Pediatric meningiomas are rare and account for only 2.2% of CNS tumors. In this age group, they are more frequently located in atypical sites, such as, mainly, the ventricular system, with a frequency of 8.8 to 13.6%. Adding this to the fact that the angiomatous subtype constitutes only 2.1% of all meningiomas, the rarity of the case reported here i s corroborated. We report a 17-year-old female patient diagnosed with intraventricular angiomatous meningioma; she underwent surgical resection of the tumor in the body and frontal horn of the right lateral ventricle, and there was no neurological sequela. With a follow-up of 4 years, there was no recurrence and the patient had clinical stability. Intraventricular tumors usually have slow growth and reach considerable size until they cause symptoms and then are diagnosed. In addition, the tumor's deep location and proximity to eloquent areas make such tumors an neurosurgical challenge. The angiomatous subtype, due to the presence of hyper vascularization (consisting of more than 50% of vascular components), may, in some cases, hinder surgical resection as well as be erroneously diagnosed. However, surgical treatment aimed at total resection of the lesion remains the conduct of choice in the case reported here, especially in patients in the first two decades of life, in which the use of radiation is avoided. Specifically when it comes to the surgery, we chose a transcallosal approach that allows a good transoperative visualization of the lesion when located in the body and frontal horn of the lateral ventricle.

GJMR-A Classification: *NLMC Code: WL 140*

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Rare Case of Young Patient with Intraventricular Angiomatous Meningioma

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Abstract- Pediatric meningiomas are rare and account for only 2.2% of CNS tumors. In this age group, they are more frequently located in atypical sites, such as, mainly, the ventricular system, with a frequency of 8.8 to 13.6%. Adding this to the fact that the angiomatous subtype constitutes only 2.1% of all meningiomas, the rarity of the case reported here i s corroborated. We report a 17-year-old female patient diagnosed with intraventricular angiomatous meningioma; she underwent surgical resection of the tumor in the body and frontal horn of the right lateral ventricle, and there was no neurological sequela. With a follow-up of 4 years, there was no recurrence and the patient had clinical stability. Intraventricular tumors usually have slow growth and reach considerable size until they cause symptoms and then are diagnosed. In addition, the tumor's deep location and proximity to eloquent areas make such tumors an neurosurgical challenge. The angiomatous subtype, due to the presence of hyper vascularization (consisting of more than 50% of vascular components), may, in some cases, hinder surgical resection as well as be erroneously diagnosed. However, surgical treatment aimed at total resection of the lesion remains the conduct of choice in the case reported here, especially in patients in the first two decades of life, in which the use of radiation is avoided. Specifically when it comes to the surgery, we chose a transcallosal approach that allows a good transoperative visualization of the lesion when located in the body and frontal horn of the lateral ventricle.

I. Introduction

Meningiomas have a progressively higher incidence with increasing age, with a mean age of presentation of 65 years. They are, therefore, the most frequently reported tumors of the central nervous system (CNS) in adulthood.[1] However, cases in children and adolescents are rare, representing 2.2 to 2.6% of CNS tumors.[1,2] In such age group, are more often located in unusual sites, such as in the ventricular system.[3]

Such intraventricular meningiomas have the particularity of being slow growing and reaching considerable size until they become symptomatic.[4] In addition, the deep location and relationship with underlying eloquent areas make tumor resection a neurosurgical challenge.[5,6] In view of this, and that the angiomatous subtype– defined as presenting more than 50% of vascular components on microscopic analysis – constitutes only 2.1% of all meningiomas, rarity is credited to the case reported here.[7] We emphasize that this is possibly the first report of a patient in the first two decades of life with angiomatous meningioma in an intraventricular site.

In this report, we aim to expose our neurosurgical experience in a case with rare variants and perform a literature review on the main aspects that we deem necessary to support our approach.

II. Case Report

A 17-year-old female patient, previously healthy, presented retro-orbital headache for 3 months, followed by blurred vision and double vision. Physical examination revealed just a convergent strabismus due to paresis of the right lateral rectus muscle. The cranial magnetic resonance (MRI) showed an expansive lesion in the frontal horn of the right ventricle, just in front of the foramen of Monro, with dimensions of 2.0 x 1.3 x 1.8 cm (AP x L x h) in the larger diameter cuts.

The lesion presented moderate hyperintensity with small hypointense foci on T2-weighted images. On T1, it was isointense, and after contrast, it showed intense and homogeneous uptake, except in the same hypointense foci on T2. There were no signs of dilation of the supratentorial ventricular system (Fig. 1 A - D). Such radiological characteristics suggested the diagnosis of intraventricular meningioma, with areas of calcification. It was considered an occasional finding, since the topography was not compatible with the presenting symptoms.

The surgical treatment was performed in the same hospitalization, due to the risk of acute hydrocephalus. The approach was made via the transcallosal route, following the steps: dorsal decubitus and head in a neutral position; bicoronal incision; right frontal paramedian craniotomy, with lateral extension of 5.5 cm from the midline and 5.5 cm from the coronal suture forward; opening the dura mater in a "C" shape, with the base facing the midline; under microscopy, dissection of the inter-hemispheric fissure and retraction of the frontal lobe with placement of the fixed spatula (on a Leyla support) on the medial surface; identification of the cingulate gyrus and pericalosal arteries; callosotomy with 1,2 cm starting from the transition between the knee and the corpus callosum; identified a grayish vegetating lesion inside the right frontal horn,

Author α σ ρ ω ¥ § χ: Department of Neurosurgery, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Brasil.
e-mail: gabriel.heemann@gmail.com

which had a soft consistency and were vascularized; resection of the lesion through coagulation and aspiration and by fragments, leaving a small residue adhered to the ependyma of the caudothalamic groove. Postoperatively uneventful and absence of new deficits, with diplopia and strabismus remaining.

Histopathological analysis and immunohistochemical painel showed extensive vascularization and low mitotic index (Ki67 less than 2%). In addition, that results were visualized: epithelial membrane antigen (EMA), positive; cytokeratin (CK), negative; progesterone receptor, negative; and glial fibrillary acidic protein (GFAP), positive (Fig.2 A-B). Thus, the diagnosis of angiomatous meningioma (WHO grade I) was confirmed. Postoperative MRI showed a small residual focus near the thalamostriate groove (Fig. 3 A-D and Fig. 4 A-D). After 6 months, the patient underwent strabismus correction with an ophthalmologist at another institution. Currently, with approximately 4 years of follow-up, she is asymptomatic and without evidence of recurrence of the residual lesion.

III. Discussion

Meningiomas are tumors that predominate in the fifth and sixth decades of life, with a mean age of presentation of 65 years.[1] In general, they represent 36.4% of primary CNS tumors and approximately 24-30% in adults.[1,8] Nevertheless, in the pediatric population, the prevalence among CNS tumors varies between 0.4 and 4.6%.2,[3,9–13] The equivalence between genders also contrasts with what occurs in the adult population, which has a female to male ratio of 2:1.[1,2,14] This difference is believed to be due, mainly in the prepubertal period, to the absence of the effect of sex hormones on corticosteroid receptors in meningioma cells.[10,15–17]

In the first two decades of life, there is a higher incidence of grade II (atypical) and grade III (anaplastic) meningiomas, according to the WHO: 9.9 and 8.9%, respectively.[2,18] They are genetically and phenotypically more aggressive with a high frequency of brain invasion.[9,14] Among the most frequent grade I meningiomas, the angiomatous subtype occurs in 2.8% of cases,[2] and in 2.1% of all meningiomas at any age.[19] Such subtype is defined when the vascular component exceeds 50% of the total area of the tumor.[7,19] However, the differential diagnosis with hemangioblastoma and hemangiopericytoma is necessary, with immunohistochemistry and morphology having essential roles in the diagnostic confirmation: low MIB-1/Ki67 index and positivity for progesterone receptor, EMA, vimetin, cytokeratin, and desmoplaquin.[7,19–23]

The characteristics of angiomatous meningiomas, due to their rarity, are covered in few studies.[7,19,24,25] They may present moderate to severe cerebral edema with a frequency of 74 to 88.9%,[7,19] due to hypervascularization, increased blood pressure. capillary permeability and secretion of VEGF (vascular endothelial growth factor).[19] On magnetic resonance imaging, they may show more signs of flow voids, rarely present necrosis and tend to have homogeneous enhancement to paramagnetic contrast.[19,23]

Meningiomas in pediatric patients present in atypical sites more frequently than in adults: lateral ventricles, skull base, posterior fossa. [2,3,10,15,26] Intraventricular location occurs in 11%, compared to 0.3-3% in all ages and 0.5-4.5% in adults.[2,10,27]

Intraventricular meningiomas (IVM) are located in 76% of cases in the lateral ventricles (most common on the left side); 16% in the third ventricle; and 7% in the fourth ventricle.[5,27] There are studies suggesting that the lateral ventricles are the preferred site for pediatric IVMs.[26,28] These originate from the choroid plexus, growing i n the t e l a choroidea.[4] The vascularization of the tumor depends on its location in the ventricle: the nutrient vessels are of small caliber and usually originate from the choroidal arteries.[27]

Clinically, pediatric IVMs are usually asymptomatic, until they reach large dimensions in the lateral ventricles, where the risk of hydrocephalus is lower. However, when located in the third or fourth ventricle, obstruction to the flow of cerebrospinal fluid can result in manifestations at early stages of tumor growth.[5,27,29,30] Therefore, symptoms– headache, nausea, vomiting and visual disturbances – are more frequently related to tumor compression and an insidious increase in intracranial pressure.[5,27,31] Indolent cognitive deficits compromising memory and attention may also occur.[32,33] Typical symptoms of an acute increase in intracranial pressure are uncommon.[29] The clinic, therefore, correlates with the location of the tumor within the ventricle, tumor size and the direction of its growth.[27] Finally, we emphasize that the clinical presentation of the reported patient – convergent strabismus due to paresis of the right lateral rectus muscle – was not correlated with the tumor. This was still relatively small in size and its location did not justify the signs and symptoms.

IVMs usually have the classic radiological appearance of other meningiomas, well-defined globular shape, however no dural tail. They are usually iso to hypotensive on T1-weighted images, hyperintense on T2-weighted images and suffer strong contrast enhancement.[16,27] Especially in the pediatric population, other more frequent intraventricular tumors can make the differential diagnosis difficult: chorioid plexus tumors, ependymoma, primitive neuroectodermal tumor, teratoma, and astrocytoma.[30,34] Chorioid plexus tumors usually affect younger than 10 years, and on MRI present a multilobulated mass with intense contrast enhancement and frond-like appearance. Ependymomas represent approximately one third of

CNS tumors in children under 3 years of age and are characterized by necrosis, hemorrhage, cyst formation, and on MRI, they are hypointense on T1 and hyperintense and heterogeneous on T2.[35]

The surgical approach of a benign IVM is a neurosurgical challenge, given its deep location and its proximity to eloquent areas and vessels in the ventricular walls.[5,34] The extent of the initial resection is an independent prognostic factor, presenting a significant association with recurrence and malignancy.[2] The patient reported here did not present a recurrence in the 4 years of follow-up, which is a result consistent with the literature. In a 2012 review, with 201 cases from different series, there were only eight recurrences;[27] however, in a meta-analysis with 677 cases of meningiomas in the first two decades, the numbers are more significant: there were 141 recurrences with an average presentation of 3.6 years and with mortality from this event in 46 cases.[2] The recurrence in this age group occurs basically in cases of atypical meningiomas and anaplastic or after partial resection.[36] Post-surgical mortality and morbidity in patients in the post-pubertal phase, as is the case of the patient reported here, are similarity to those observed in cases of meningioma in adults.[2] The use of adjuvant radiotherapy should be avoided in young patients, opting for serial evaluation and reoperation in case of recurrence.[2,3,8–11,14,18,37]

In the literature, there are several surgical approaches for IVM resection: temporoparietal, transfrontal, middle posterior temporal gyrus, posterior inferior temporal gyrus, parieto-occipital and transcallosal.[5,34] The choice is individualized and based on the location of the tumor within the ventricle, in tumor size and its vascular network, always with a objective of preserving the adjacent brain tissue, performing small corticectomy and retracting little as possible.[5,6,27,30,33,34] The justification for the choice the approach is determined by the option that allows better access to the longest axis of the lesion, to minimize transcortical transgression, by the spectrum of preoperative neurological deficits, proximity to the eloquent structures, in addition to anatomical knowledge of the cortical and white matter.[29] We chose the transcallosal approach because it allows better access to the frontal horn and lateral ventricle body. This approach prevents cortical damage; however, some care is needed with the possible presence of tributary cortical veins tributary of the superior sagittal sinus, which can be anticipated in preoperative examinations, and with the corpus callosum, which must be distinguished from the cingulate gyrus by the change in color.[5] Despite the degree of difficulty, IVM surgery has shown low morbidity and mortality rates in recent decades, and most postoperative complications– visual deficits and praxis– are temporary.[27,29,34] These low rates are consistent with the case reported here, which postoperative complications or sequelae did not occur.

IV. Conclusion

Intraventricular angiomatous meningioma is a rare entity, even more in patients in the first two decades of life. The clinic is nonspecific in most cases, making MRI evaluation necessary for the diagnosis and definition of the surgical approach, and the histopathological analysis is what defines the diagnosis of the angiomatous subgroup. Surgical resection is the treatment of choice. However, the goal of total resection should not be above the goal of preserving the patient's functions and quality of life.

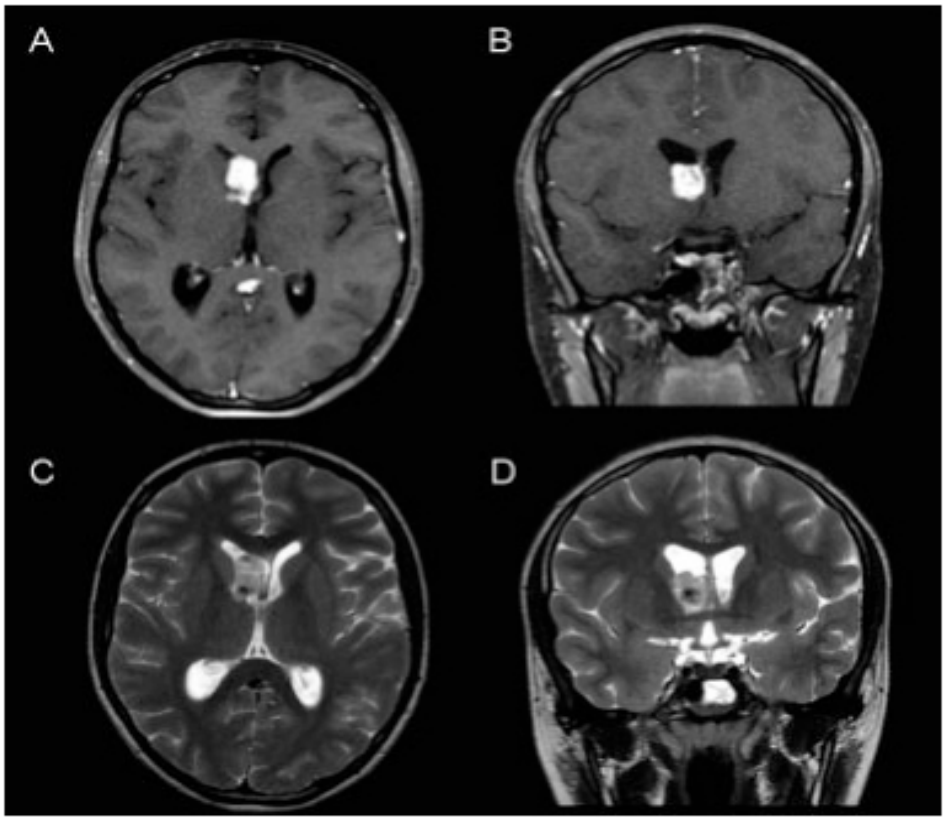

Figure 1: Preoperative MRI: A and B – T1 with gadolinium, axial (A) and coronal (B). Lesion with intense uptake at the level of the right frontal horn, close to the foramen of Monro. C and D – T2 axial(C) e coronal(D). Hyperintense lesion, with a focus of hypointense calcification (also seen in A).

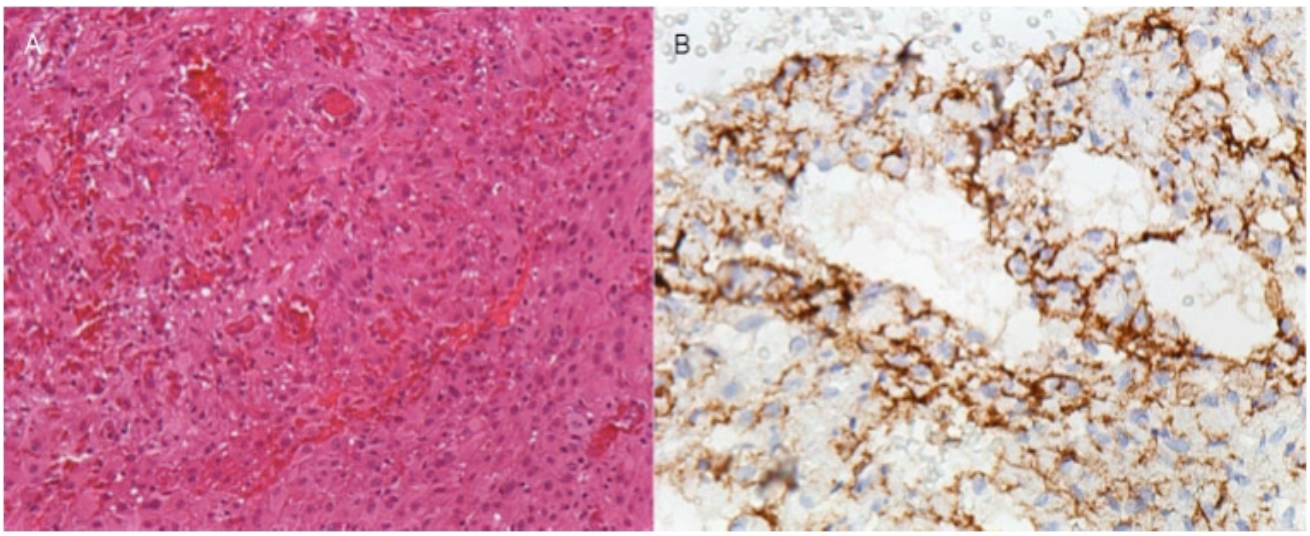

Figure 2: A – Hematoxylin and eosin staining, 200 times magnification: image showing histopathological features of meningioma and significant vascular component. B – Immunohistochemistry, 400-fold magnification: tumor cells showing positivity for EMA.

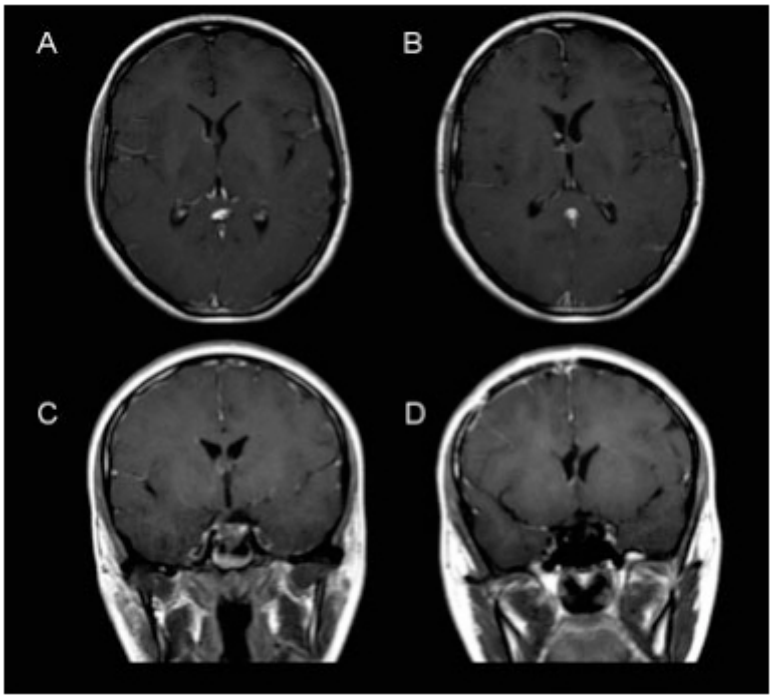

Figure 3: Postoperative MRI: T1 with gadolinium, axial (A and B) and coronal (C and D) planes. Small residual focus near the foramen of Monro, attached to the thalamostriate vein (identified during the transoperative period).

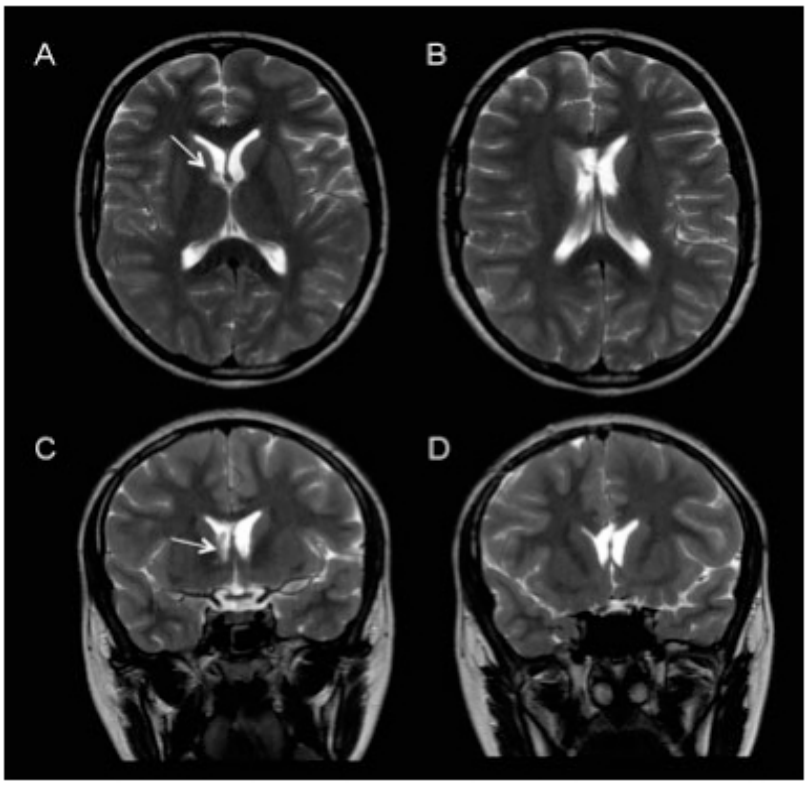

Figure 4: Postoperative MRI: T2 axial (A and B) and coronal (C and D). Small residual focus at the level of the foramen of Monro (arrows).

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Neuropathic Pain: Basic to Advanced Neuropathic Pain

By Santosh Nagare
Banaras Hindu University

Abstract- As we know that pain is the most common reason for which a patient takes medicine. Pain is not a single entity but may be classified as nociceptive pain, inflammatory pain, and neuropathic pain. Nociceptive pain such pain can be healed or cured by using NSAIDs and other analgesics. Neuropathic pain is caused by the direct lesion on the neuron or damage or dysfunction of peripheral or central neurons. Minor neuropathic can cured automatically because peripheral nervous systems neuron surrounded by Schwann cell which promotes the healing of neurons but CNS neurons don't have Schwan cell they are covered with oligodendrocytes which don't have self healing property so pain mediated through CNS are generally chronic. Even the smallest stimulation results in spontaneous intense pain after that it gets transformed into chronic pain syndrome which is difficult to treat.In chronic pain syndrome, plastic changes occur in nociceptive neurons which cant be reversed by pharmacological treatment. In this review, we have discussed the core pathophysiology of neuropathic pain and advances in it to date.

Keywords: *neuropathic, NSAIDs, oligodendrocytes, chronic.*

GJMR-A Classification: *NLMC Code: WL 103.5*

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I. Introduction

Steps In Neuronal Signal Processing: Sequence process occurs between pain initiation and the pain experience through ascending pathway[1].

1. Transduction: It's the process by which a noxious signal gets transformed into an electrical signal so that it is carried towards the brain. In neuropathic, there is lesion or damage to the neurons so this mechanism is continuously on to produce the noxious signal. In the case of neuropathic pain when the nociceptor gets sensitized due to a signal it may recruit another silent receptor so that pain gets amplified this phenomenon is called Hyperalgesia. This afferent neuron sensitization is blocked by morphine by hyperpolarizing afferent neurons[2]. Neurons of this phase are termed as 1st order neurons.
2. Transmission: The phase ion which noxious stimulus is carried or transmitted towards the spinal cord then to the thalamus and cortex. For transmission there two main primary afferent nociceptive neurons which conduct signal according to stimuli with different speed.

C- Fibers

- Nonmyelinated
- Signal conducting range 0.5-2m/sec
- Sensitive to mechanical, thermal, chemical stimuli hence called C-polymodal nociceptors.

A-delta fibers

- Thin
- Myelinated
- Signal conducting range 2-20m/sec
- Generally, respond to only high threshold mechanical stimulation because to open such fibers strong stimulus is required to initiate and transmit the noxious signal. Because they require high potential to activate called High Threshold Mechanoreceptors.
- Some delta fibers respond to thermal stimuli also termed Mechano-thermal receptor.
- Neurons of this phase are termed second-order neurons and sensitization of these neurons called central sensitization leads to hyperalgesia and allodynia later.

Modulation: In this step, the noxious stimuli are modified intermediate neurons within the spinal cord and descending inhibitory system. Opioids act at the level of the spinal cord and inhibit dorsal horn neurons[3]. But beyond this morphine also produce its effect through periaqueductal central gray, medullary raphe, and spinal trigeminal nucleus too[4].In the case of neuropathic pain descending inhibitory system is dysfunctional.

➢ Descending Modulatory system: This system activated at the level of periaqueductal (PAG) of the midbrain and these neurons then project downwards towards the medulla(nucleus reticularis gigantocellularis, nucleus raphe Magnus) and locus cerulus which is the major source of NE[5]. The name of the pathway is descending inhibitory pathway itself indicates that it will inhibit the signal by promoting the release of neurotransmitters.

Corresponding Author: (M.Pharm), Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, Uttar Pradesh, India.
e-mail: santoshnagare11061997@gmail.com

The distinct mechanism of Descending pain inhibitory pathways:

1. Descending neurons have direct contact with pain relay neurons of the spinal cord so electrical stimulation of the brainstem causes hyperpolarization of nociceptive receptors in the spinal cord and the release of neurotransmitters in descending pathway produces the inhibitory effect on ascending pathway so pain signal gets blocked at the spinal level.
2. The central terminal of the primary afferent neuron lies in the spinal cord and the central nociceptive receptor for neurotransmitter release in the spinal cord only by descending axon. To this postsynaptic response evoked by dorsal root at lamina 2 reduced by NE.
3. Superficial laminas of the spinal cord contain interneurons which contain inhibitory neurotransmitters like GABA, Glycine, Enkephalin. Descending pathway excites these interneurons of the spinal dorsal horn this will inhibit the ascending pain signal.

Perception: From second-order neurons, the signal is handover to the 3rd order neurons. Third-order neurons project to the somatosensory cortex and enable perception of pain through different parts[6]. only Opioids able to inhibit pain perception no other drug able to do this.

II. Pathophysiology of Neuropathic Pain

Diseases which causes spinal cord lesion are spinal cord injury, syringomyelia, multiple sclerosis, transverse myelitis, and neuromyelitis optica[7]. Peripheral neuropathies diabetes mellitus, HIV[8] and Leprosy, chemotherapy, immune and inflammatory disorder. Because of peripheral nerve lesion, there is an alteration in electrical properties of the sensory nerve which create the imbalance between the central excitatory and inhibitory system leads to complexity and chronic neuropathic pain.

Peripheral Sensitization: This means the sensitization is limited to the periphery only or the sensitization in which the brain and spinal cord are not involved.

Primary afferent neurons C-fibers and A-delta fibers are involved in peripheral sensitization these nociceptors respond best to the noxious stimuli. These pathophysiological changes are accompanied by cellular and molecular changes. The spontaneous activity of the injured nerve exactly matches with the expression of mRNA to increase the population of voltage-gated sodium channels. This increase in the population of voltage-gated sodium channels leads to the lowering of threshold potential. Now, this cluster of sodium channel not only accumulate at injured nerve but also to the proximity of dorsal root ganglia[9]. So that's why pathophysiological changes in DRG are of particular therapeutic interest because DRG doesn't have BBB so it's easily accessible for systemic therapies[10]. Damage to peripheral nerve leads to upregulation of various receptor proteins which are expressed in very less quantity in normal physiology[11]. Ex. Vanilloid receptor (TRPV1), TRPV4. There are shreds of evidence that uninjured fibers also contribute to the pain signaling with injured fibers[12] Product Such as nerve growth factor are released in the vicinity of the nerve fibers that might trigger the release of TNF alpha and expression of the sodium channel, TRPV1, Adrenoreceptor thereby converts normal fibers into abnormal ones[13].

III. Central Sensitization

Sensitization in the spinal cord– As a consequence of peripheral sensitization secondary changes occurs in the spinal cord dorsal horn. Peripheral neuronal damage leads to an increase in excitability of wide dynamic range neurons(WDRN). Wide dynamic range neurons are the neurons that respond to both painful and non-painful stimuli[14]. These neurons behave or work in graded response means as the strength of noxious stimulus increases results in increased pain sensation. This leads to hyperexcitability called central sensitization. This sensitization is maintained by pathological C-fibers by sensitizing the spinal cord dorsal horn to release glutamate act on postsynaptic NMDA receptor and neuropeptide substance P[15]. Central sensitization is maintained by an intracellular cascade of mitogen-activated protein kinase(MAPK)[16]. As soon as central sensitization is established then a small stimulus will responsible for the activation pain signal through low threshold A-beta and A-delta mechanoreceptor[17]. Central N-type of calcium channel located presynaptic membrane of primary afferent neuron plays important role in central sensitization by facilitating glutamate and substance P release[18].

Advances in Neuropathic Pain Pathophysiology (Receptors and Mediators)

- Toll-like receptor 7

Toll-like receptor 7 contributes to neuropathic pain by activating NF-κ Binprimary sensory neurons. Toll-like receptors (TLRs) are a family of transmembrane pattern recognition receptors that mediate innate and adaptive immunity by recognizing exogenous ligands, pathogen-associated molecular patterns(PAMP), and danger-associated molecular patterns(DAMPs)[19]. TLRs not only expressed by the immune system but also neurons and nonneuronal cells express this receptor. To explore the potential role of DRG TLR7 in neuropathic pain, they examined whether TLR7 expression was altered in DRG and spinal cord following unilateral L4

SNL, and results revealed that SNL, but not sham surgery, led to the time-dependent increases in expression of Tlr7 mRNA and its protein in the ipsilateral L4 (injured) DRG on days 3, 7, and 14 post-SNL. So they have further studied blocking of these TLR7 attenuates the pain hypersensitivity. so this overall result shows that DRG overexpression of TLR7 leads to neuropathic pain symptoms[20]. Increased expression of TLR7 increases the activation of NF-Kb in injured DRG leads to neuropathic pain symptoms.

- TLR8 in the Trigeminal Neuropathic Pain in Mice

TLR8 is located in the intracellular endoplasmic reticulum (ER), endosomes, and lysosomes of DRG neurons, and plays an important role in the pathogenesis of spinal nerve injury-induced neuropathic pain[21].TLR8 is mainly expressed in DRG and its expression is upregulated after SNL. Concluding pieces of evidence shown that TLR8 is necessary for maintaining neuropathic pain. This is achieved by delivering siRNA which will exclusively attenuate the TLR8 mediated pain state like mechanical allodynia and hyperalgesia. The results have been shown that TLR8 Expression is Increased in TG Neurons After pIONL-Induced TNP. Deletion of *Tlr8* Reduces the pIONL-Induced Activation of ERK and p38, and the Expression of Pro-inflammatory Cytokines in the TG. Intra-TG Injection of TLR8 Agonist VTX-2337 Induces Pain Hypersensitivity. TLR8 Agonist VTX-2337 Increases the Ca^{2+} Concentration in TG Neurons[22].

- TLR signaling adaptor protein MyD88 in neuropathic pain.

The myeloid differentiation factor-88 adaptor protein (MyD88) mediates most TLRs (except for TLR3) signaling, as well as Toll/Interleukin receptor domain signaling through the interleukin (IL)-1 and IL-18 receptors. This protein in primary sensory neurons contributes to persistent inflammatory and neuropathic pain along with neuroinflammation. Studies have shown that selective deletion of *Myd88* in $Na_v1.8$-expressing primary sensory neurons in CKO mice leads to reductions incomplete Freund's adjuvant (CFA) induced inflammatory and chronic constriction injury (CCI) induced neuropathic pain in the maintenance phase, without affecting basal painand acute inflammatory pain[23].

- Sphingosine-1 phosphate receptor- 1 in neuropathic pain

S1PR1 Activation in astrocytes contributes to neuropathic pain. Based on genetic and pharmacological inhibition of S1PR1 with the different antagonists from different classes attenuated or even reversed neuropathic pain. S1PR1 Antagonist retains their capability to inhibit neuropathic pain without affecting endogenous circuitry. However, this is limited to astrocyte-specific activation of S1PR1[24]. In addition to this administration of selective S1PR1 agonist SEW2871[25] caused the development of mechano-hypersensitivity in naïve mice[26]. S1P antagonism by FTY720/fingolimod results in a decreased chemotherapy-induced neuropathic pain[27]. Fingolimod also able to reduce the neuropathic pain in MS by inhibiting S1PR1 dependent central sensitization of the dorsal horn[28].

- P2X4 receptor in neuropathic pain

A new concept of evoking neuropathic pain was proposed in which spinal microglia are activated after PNI(Peripheral Nerve Injury), and P2X4Rs on these activated microglia have an important role in evoking neuropathic pain[29]. P2X4 Receptor role in neuropathic pain is well established. The SNRIs duloxetine has an inhibitory effect on the function of microglial P2X4R so it's used in neuropathic pain treatment. Duloxetine inhibited microglial P2X4R function in addition to that Intrathecal administration of duloxetine attenuates mechanical allodynia after PNI(Peripheral Nerve Injury) that may be because of possible involvement ofP2X4R[30]. Upregulation of this ion gated receptor P2X4Rs is might be connected to fibronectin/ integrin-dependent mechanism based on finding made on echistatin which blocks beta1 and beta3 integrins. In vitro studies have shown that echistatin down regulates the P2X4Rs upregulation[31]. P2X receptors are non-selective cation channels that open in response to ATP binding, allowing the rapid flow of ions (K^+, Na^+, Ca^{2+}) across the membrane but the calcium permeability is highest in the case of P2X4Rs, and stimulation of these receptors leads to the activation of p38 MAPK. This results in p38 MAPK activation and BDNF release as a key step in microglia-neuron communication leading to nerve injury-induced pain hypersensitivity[32]. This signaling further activates PLA_2 liberating arachidonic acid (AA) and release of prostaglandin E2 (PGE_2) that leads to hypersensitivity of peripheral pain pathways[33].

- PARP-1- Regulated TNF-Alpha expression in Neuropathic pain

Poly-(ADP-Ribose) Polymerase 1 a Transcription regulator for TNF-Alpha. Its expression in DRG and SDH(Spinal Dorsal Horn) contributes to neuropathic pain pathogenesis in rats. This has the basis of lumbar 5 nerve ligation (L5 SNL) resulted in increased expression and activation of PARP-1 in DRG and the spinal dorsal horn[34]. PARP-1 Inhibitors impaired neuropathic pain states indicate their role in neuropathic pain. Studies have shown that PARP-1 involved in the regulation of inflammatory processes and functionally associated with transcription factor NF-Kappa B contributes to chronic inflammatory diseases[35].

- CCL2 (monocyte chemoattractant protein-1, MCP-1) in Neuropathic Pain

Activation of spinal microglia plays a critical role in neuropathic pain. Studies have shown that intrathecal CCL2 leads to spinal microglial activation and a neuropathic pain-like state. This acts as a precursor for understanding the further role of CCL2. Neutralizing Antibodies against CCL2 lead to inhibition of neuropathic pain behavior and microglial activation[36]. Thus CCL2 is involved in immune activation and maintaining sensitivity in neuropathic pain. Ryk (receptor-like tyrosine kinase) mediates excitatory synaptic transmission and also releases CCL2 in neuropathic pain and antagonism of RyK leads to decreased CCL2[37]. So because of this role modulation or inhibition of CCL2 responsible for attenuation of neuropathic pain. Minocycline is under study for neuropathic pain and its already been proven that it acts through down regulating microglial activation through CCL2 and CCR2[38].

- Melanocortin Type-4 Receptor in Neuropathic Pain

Melanocortin type-4 receptor is stimulated after nerve injury by α-MSH (Melanocortin Stimulating Hormone). This result in tonic pronociceptive response leads to sustaining the neuropathic pain. This idea leads to the development of a bifunctional compound which will act as an agonist on opioid receptor and antagonist of MC4 (Melanocortin 4 Receptor). Such compound produced effect at very low dose without affecting motor coordination in CCI mice[39]. It also investigated that MC4 Antagonism produced analgesia, anti-allodynic, anti-nociception and this observation further strengthen by Ligands VVK052 and VVK054 which show excellent affinity towards the human MC4 Receptor[40]. Tolerance in the case of opioid therapy is obvious the use of bifunctional ligand also shown the capability to decrease the tolerance[41]. These results showed the possibility of the melanocortin system and its receptor in neuropathic pain. Withdrawal symptoms and α-MSH induced hyperalgesia attenuated by the melanocortin-4 Receptor antagonist. The widespread distribution of melanocortin might be widely associated with neuropathic pain[42]. So prolonged blockade of melanocortin receptor (most probably MC4) results in alleviation or decreased of allodynia in rats with neuropathic pain[43].

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Predictors of Depression and Well-Being in Caregivers of Young Children with Developmental Delays in Vietnam

By Son Nguyen Duc, Jin Y. Shin, Karleigh Groves, Martha Chaiken & Amanda Leonard

Hofstra University

Abstract- The present study examined the impact of social support and other variables on depression experienced by the caregivers of young children with developmental delays in Vietnam. We conducted a survey of 109 caregivers of children with developmental delays who were enrolled in kindergarten programs in Hanoi, Vietnam. The survey included questionnaires on the availability of informal and professional support, perceived social support, and depression. The results suggest that the more the caregivers felt that they received support, the less depression they experienced. However, the amount of informal or professional support was not significantly related to depression. The more maladaptive behaviors their children manifested, the more depressed the caregivers were. The findings suggest that there is a need for services and supports that not only help caregivers to be effective parents but also address feelings of distress that stem from parenting children with disabilities.

Keywords: children with developmental delays, caregivers of children with developmental delays, developmental disabilities, social support, depression, Vietnam.

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Son Nguyen Duc [α], Jin Y. Shin [σ], Karleigh Groves [ρ], Martha Chaiken [ω] & Amanda Leonard [¥]

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I. Introduction

Parents of children with disabilities experience increased parenting stress due to the caregiving demands the children place on them. Not only do the children fall behind their peers intellectually, but to the extent that their behaviors are maladaptive and inappropriate for their age norms, this will place demands on the caregivers who must learn special ways of raising them. As a result of parenting stress, caregivers of children with disabilities are at an increased risk for depressive symptoms compared to other groups [1–5].

Author α: Ph.D, Department of Psychology and Pedagogy, Hanoi National University of Education, Hanoi, Vietnam.
e-mail: nguyensontlhnue.edu.vn@gmail.com
Corresponding Author σ: Ph.D., Department of Psychology, Hofstra University Hempstead, NY, USA.
e-mail: jin.y.shin@hofstra.edu
Author ρ ¥: B.A., Department of Psychology, Hofstra University, Hempstead, NY, USA. e-mails: kgroves1@pride.hofstra.edu, aleonard2@pride.hofstra.edu
Author ω: Ph.D., Department of Psychology, Hofstra University, Hempstead, NY, USA. e-mail: marthaleah.chaiken@hofstra.edu

Olsson and Hwang[3] examined whether the increased stress among parents caring for children with disabilities has negative effects on their mental health. Two hundred sixteen participants were recruited using letters mailed to families enrolled in community-based programs for families with disabled children in Sweden. Of the 216 families, 151 children were diagnosed with an intellectual disability without autism, and 65 children were diagnosed primarily with autism. The control group was composed of 214 families with typically developing children of the same geographical area, age, and gender distribution, which the researchers identified using the National Office of Statistics. They found that depressive symptoms were more common among the mothers of children with disabilities than those of children without disabilities. In addition, mothers of children with autism had the highest levels of depression compared to mothers of children with intellectual disabilities without autism, who in turn had higher levels of depression than the control group. Elevated depression scores beyond the cut-off point for clinical depression based on a standardized scale for depression were more common in mothers of children with autism than in mothers of children with intellectual disabilities without autism, who had more elevated scores than the control mothers. Mothers of children with disabilities had overall higher depression scores than fathers of children with disabilities.

Zeedyk and Blacher [5] considered the different impacts that child disability and child behaviors have on maternal depression over time. The participants included 223 families of children with and without intellectual disabilities drawn from a large multisite study across three different universities in Southern California and Pennsylvania in the U.S. The children were three years old when the families were recruited. They were followed up as the children moved through adolescence. This study found that over the long term, child behavior problems made a greater contribution to maternal depressive symptoms than did child disability status. The study also found that greater child behavior problems, higher financial impact, and lower levels of dispositional optimism were significantly related to higher initial depressive symptoms for mothers. However, only increased child behavior problems had a significant impact on changes to ongoing depressive

symptoms. As the child moved into adolescence, they found that prior levels of depression for the parent and financial impact were related to greater depressive symptoms.

Support from others can help relieve the psychological and physical strain caregivers experience. The types of support could range from the education provided by teachers, babysitting provided by neighbors, or the willingness of friends to listen to the concerns the caregivers have about their children. It has been widely documented that social support influences the successful adaptation of such families who have children with disabilities and buffers the stress they experience in caring for children with disabilities[1,6,7].

Zaidman-Zait et al. [8] studied mothers of children with autism spectrum disorder by compiling data at the time of the child's diagnosis with autism spectrum disorder and then again after two years. The data were drawn from Pathways in ASD, a large Canadian multisite longitudinal study examining the developmental trajectories of children with autism spectrum disorder. When the cohort of 283 mothers was recruited, the children's ages ranged from 2 to 4, and they had been recently diagnosed with ASD. The study found that higher levels of perceived social support by mothers were correlated to lower levels of stress at the time of diagnosis. After two years, it was found that high parenting stress at the time of the child's diagnosis was predictive of increased parenting stress, but higher levels of perceived social support at the time of diagnosis and increased perceived support over time were predictive of decreased parenting stress after two years.

Halstead et al.[7] identified behavioral and emotional problems of children with developmental disabilities as significant stressors for family members. They also examined whether perceived social support, positive perceptions or coping style could explain some of the variability in the stress the mothers of these children experienced. Participants consisted of 138 mothers whose 4- to 18-year-old children were diagnosed with either autism, Down syndrome or cerebral palsy in England. They found that perceived social support was the only moderating factor, with a statistically significant relationship with life satisfaction, depression, and positive affect for mothers of children with developmental disabilities.

A study conducted by Oh and Lee [9] examined the relationship between social support and caregiver burden in South Korean mothers of children with developmental disabilities. The participants in this study were recruited from different special education programs, community welfare centers, mental health agencies, and local parents in Seoul, totaling 187 mothers of children (M = 10.35 years) with developmental disabilities. Results indicated that the mothers had strong positive perceptions of emotional support from family and friends; however, they perceived low levels of social support in terms of tangible assistance and immediate help. Furthermore, participants reported perceiving low levels of social support from extended family, friends, social groups, and service organizations. Mothers reported positive contributions and high levels of support from their children's fathers, which was moderately correlated with low levels of caregiver burden. The results showed that social support explained the greatest variance in burden compared to child disability characteristics and mother's socio-demographic characteristics.

Like many other countries in Asia, Vietnam is a collectivistic culture in which filial piety is respected and a greater emphasis is placed on interdependent relationships than on the independence and autonomy of individuals [10]. Often, individuals are expected to sacrifice their needs for the benefit of the group and to meet collectivistic goals. For example, children are expected to do well in school to meet the expectations of their parents, and wives are expected to raise children to meet the expectations of their families. When they fail to do so, they often experience blame and guilt. Negative perceptions and attitudes prevail toward individuals with disabilities, and these are often extended to their mothers and families as not raising their children properly [10,11].

A few research studies conducted in Vietnam have found that Vietnamese parents of children with intellectual disabilities are stressed [12,13]. Vietnamese mothers of young children with developmental delays are more stressed than those of children without delays[12]. Shin et al.[11] examined parenting stress experienced by mothers and fathers of young children with cognitive delays in Vietnam. The participants consisted of 106 mothers and 93 fathers in Hue city whose children met the criteria of cognitive delays based on the opinions of kindergarten teachers who worked with them and a screening test. They found that mothers were more stressed than fathers. Neither the availability of informal nor professional support was relatedto parenting stress for mothers, but fathers who reported greater availability of informal and professional support experienced less parenting stress. Perceived social support was not related to parenting stress for either mothers or fathers.

In this study, we examined the experience of depression among the caregivers of children with developmental delays in Vietnam as related to social support. As a result of ongoing parenting stress while adequate educational and support systems are not yet fully in place, caregivers might be at risk for depressive symptoms. Depression occurs when the ongoing challenges of caregiving become too overwhelming. With no one to turn to for adequate help, the caregivers begin to wear down and to lose hope and a sense of meaning in life. It was speculated that the ongoing

parenting stress of coping with their children may wear the caregivers down and make them struggle with the fundamental existential meaning of their lives rather than deriving joy from life and feeling pride in raising their children. It was hypothesized that caregivers who received higher levels of social support would experience a lower level of depression. Social support was assessed in terms of the perception and availability of informal and professional support.

II. Method

a) Participants

The participants in the study were 109 caregivers of children with developmental delays from Hanoi in Vietnam. Demographic characteristics of the children and caregivers are provided in Table 1. We recruited 116 children with developmental delays and their families from kindergarten programs, which are equivalent to preschool and kindergarten programs in the U.S. These children were identified by their classroom teachers as having developmental delays and being intellectually slower than their peers, based on the teachers' observations. All the children were evaluated with the *Scales of Independent Behavior-Revised Early Development Form* (SIB-R)[14], and six children who scored above the 40th percentile were omitted from the study. A total of 109 caregivers whose children's ages ranged from 3 to 8 were included in the data analyses. Forty-two of the caregivers (38.5%) did not have information on the diagnosis of their children. Among the 67 caregivers (61.5%) who had such information, 11 (10.1%) had children who had been diagnosed with ADHD, 17 (15.6%) with autism, 15 (13.8%) with developmental delays, 12 (11%) with intellectual delays, and 12 (11%) with language delays. Among the caregivers who participated in the survey interview, 82 were mothers (75.2%), 19 (17.4%) fathers, 6 (5.5%) grandmothers and 2 (1.8%) grandfathers.

All the caregivers were interviewed by a trained post-doctoral fellow in psychology. The study protocol was approved by the IRB of the university in the U.S. where the co-authors work. The consent form was explained by the interviewer and signed by the participants before the interview.

Table 1 summarizes relevant demographics for the families of the children in the study. There were approximately twice as many male as female children. With respect to the level of education, 91% of the mothers of children with delays had completed either university or junior college education. Most of the parents were married (94.5%) with the divorce rate very low (2.8%), and more than half of the families (66.1%) were living with only their immediate family members, while 26.6% were living with other family members in addition to immediate family members.

Table 1: Descriptvie Statistics on the Characteristics of Sample Families (n=109)

Child Characteristics		Family Characteristics			
Age		Mother's Education (%)		Perceived Support based on MSPSS	
Mean	5.01	Secondary School	2.8	Mean	26.62
Range	3.00-8.00	High School	9.2	Range	14.00-36.00
SD	1.56	Junior College	27.5	SD	4.76
Gender (%)		University	56	Informal Support based on SSSPCD	
Female	25.7	Post Graduation	4.6	Mean	3.51
Male	74.3	Father's Education (%)		Range	0-10.00
Child Functioning Weighted Score based on SBIR		Secondary School	3.7	SD	2.02
Mean	454.76	High School	15.6	Professional Support based on SSSPCD	
Range	431.00-485.00	Junior College	12.8	Mean	5.03
SD	14.37	University	58.7	Range	1.00-12.00
General Maladaptive Index based on SBIR		Post Graduation	7.3	SD	2.44
Mean	-3.5	Marital Status of the Child's Parents (%)		Social Support Total based on SSSPCD	
Range	-29	Married	94.5	Mean	1.51
SD	7.65	Divorced	2.8	Range	0-5.00
		Separated	1.8	SD	0.86
		Single	0.9	Depression based on CESD	
		Caregiver's Relationship to the Child (%)		Mean	17.17
		Mother	75.2	Range	0-37.00
		Father	17.4	SD	8.47
		Grandmother	5.5		
		Grandfather	1.8		

Family's Housing Status (%)	
Independent Housing	66.1
Shared Housing with Other Family Members	26.6
Shared Housing with Non-Family Members	7.3
Economic Status of the Family	
Poor	15.6
Average	82.6
Rich	1.8

The economic status of the family was rated as being very poor, poor, average, or rich by the interviewer who conducted the home visit interviews and who examined the physical environment of the house. Families were considered rich when they had a large house with multiple floors and many high-quality possessions, such as cars, motorcycles, air conditioners, and a living room with a set of couches and a dining table set. When families had a spacious house with a robust structure and had enough possessions, such as motorcycles, refrigerators, televisions, and multi-rice cookers, they were considered middle income. Families were regarded as poor when their houses were not solid and not made of brick, had metal roofing, and some of the household materials were not of good quality. Families were considered very poor when their houses were made up of poor-quality brick and bamboo wattle with metal roofing or when they were living in the house of their relatives. Families that were considered very poor also did not have enough household materials. The majority of the families (82.6%) were rated as middle income, followed by poor (15.6%) and rich (1.8%). None of the families were rated as very poor.

III. Measures

Demographic characteristics: We included information on the child's age, gender and diagnosis. We asked about the education, occupation and economic status of the available caregivers.

Social support: We measured both the informal and professional support available to the caregivers as well as their perceived social support. *The Social Support Scale for Parents of Children with Developmental Disabilities* (SSSPCD)[15] was used to assess the availability of informal and professional support for families of children with developmental delays in Vietnam. This instrument was adapted so that it would be culturally relevant to Vietnamese families[11] and could be easily administered by professionals who work with these families. According to this instrument, 13 types of informal support and 8 types of professional support were available for Vietnamese families of children with developmental delays.

The sources of informal support consist of spouse, wife's father, wife's mother, husband's father, husband's mother, wife's siblings, husband's siblings, sons, daughters, other relatives, friends, neighbors, and other parents of children with developmental delays. Professional support can come from eight different sources: teachers, therapists, doctors, private therapists, home-helpers, social agencies, babysitters, and doctors in community health clinics. A source is designated as therapist or private therapist, doctor or doctor in a community health clinic depending on whether a fee is paid for the service. In this study, private therapists and doctors are those that require a fee.

The perceived social support was measured with the *Multidimensional Scale of Perceived Social Support* (MSPSS).[16] The scale consists of 12 items that measure three components of social support: support from a special person, from family, or from a friend. The construct, convergent and discriminant validities of the scale have been demonstrated [16], and it has adequate internal reliability (.88) and stability over time (.95)[17]. The scale has been used in a variety of international contexts [18,19]. We simplified the original seven Likert response categories to *not at all* (1), *sometimes* (2), and *always* (3). Possible scale values range from 12 to 36, with a higher score indicating more perceived social support. The Cronbach alpha reliability of the instrument in this study was .85.

Depression: Depression among caregivers was measured by using the *Center for Epidemiologic Studies Depression Scale* (CES-D)[20]. CES-D is a 20-item self-report scale that assesses the frequency of reported depressive symptoms of caregivers in the previous week (e.g., "I was bothered by things that don't usually bother me."). The CES-D is a widely used and internationally adapted scale for screening and assessing depressive symptoms in outcome studies of caregivers as well as of general and patient populations. The scale also has well-established reliability and discriminant validity for general and patient populations. The reliability of the scale in this sample was .74.

Child Behavior: The Scales of Independent Behavior-Revised Early Development Form (SIB-R)[14] was used to

assess the child's adaptive and maladaptive behavior. Parents answered 40 items regarding their child's adaptive behavior, including communication, eating, dressing, and social and motor skills. Parents also were asked to indicate whether their child engaged in eight domains of problem behavior and to rate both the frequency and severity of the behavior. Standard scores on adaptive behavior and General Maladaptive Index (GMI) scores were calculated using the procedures outlined in the SIB-R manual. The reliability of the adaptive behavior scale in this sample was .95 and that of the maladaptive behavior scale .86.

All of the scales used in this study except SIB-R were validated in Vietnamese [11,12]. In creating the Vietnamese version of SIB-R, the scale was evaluated for content and semantic equivalence of the Vietnamese and English versions. Content equivalence is established when the content of each item of the scale is relevant to the phenomena of each culture being studied [21]. Three bilingual Vietnamese rated each item on a 3-point scale as 1 (relevant to the Vietnamese culture), 2 (somewhat relevant to the Vietnamese culture) or 3 (not relevant to the Vietnamese culture). The few items that were rated as somewhat relevant were considered for rewording. Reworded items were re-examined using the same technique. For evaluation of semantic equivalence of the measurement, three bilingual Vietnamese rated each item on a 3-point scale, from 1 (exactly the same meaning in both versions), 2 (almost the same meaning in both versions) to 3 (different meaning in each version). Items rated as different meaning were considered for rewording, and reworded items were re-examined using the same technique.

IV. Results

a) Social support

The caregivers scored an average of 3.5 (SD = 2.02) out of a possible 13 on the SSSCDD subscale that measures the amount of available informal support and 1.5 (SD = .86) out of a possible 8 on the subscale that measures the amount of available professional support. The largest proportion of informal support was from spouse (91.7%), followed by husband's mother (52.3%), wife's mother (41.3%), husband's father (37.6%), wife's father (29.4%), wife's sibling (17.4%), parents of other children with delays (16.5%), friend (16.5%), husband's sibling (15.6%), neighbor(13.8%), son (7.3%), daughter (5.5%), and other relative (3.7%). The largest proportion of professional support was from private therapist (91.7%), followed by teacher (27.5%), doctor, (12.8%), home help (7.3%), hospital therapist (6.4%), doctor in community clinic (2.8%), and babysitter (1.8%). For informal support, the majority of the caregivers were relying on support from their spouse, and a significant proportion relied on their own parents and parents-in-law to help raise the children with delays. For professional support, almost all the families hired a private therapist to work with their children. In contrast, only a quarter of the families stated that teachers were available to educate their children. Those with a greater amount of informal support tended to have a greater amount of professional support available to them, r (105) = .32, p<.001.

Table 2: Types and availability of informal and formal social support (n = 109)

	Availability	Percent (%)
Informal Support		
Spouse	100	91.70
Wife's Father	32	29.40
Wife's Mother	45	41.30
Husband's Father	41	37.60
Husband's Mother	57	52.30
Husband's Sibling(s)	17	15.60
Wife's Sibling(s)	19	17.40
Son(s)	8	7.30
Daughter(s)	6	5.50
Other Relative(s)	4	3.70
Friend(s)	18	16.50
Neighbor(s)	15	13.80
Parents of Other Children with Delays	18	16.50
Formal Support		
Teacher	30	27.50
Hospital Therapist	7	6.40
Doctor	14	12.80
Private Therapist	100	91.70
Home Help	8	7.30
Babysitter	2	1.80
Social Agency	0	0
Doctor in Community Clinic	3	2.80

There was a significant relationship between the amount of informal support and the amount of perceived support based on the MSPSS, r (106) = .19, $p<.05$. The caregivers who listed more people as being available to provide informal support perceived a higher level of social support. However, the amount of professional support was not related to perceived social support, r (106) = .12, $p>.05$.

b) Depression

The degree of depression reported by the caregivers is alarming, with the mean CES-D score elevated beyond the cut-off point of 16 that indicates a risk of clinical depression (M = 17.17 SD = 8.47). Out of 109 caregivers, 61 (56%) were suspected of being clinically depressed. We further investigated the characteristics of these caregivers by examining the diagnoses of their children. Unfortunately, 42 (19%) out of the 109 caregivers did not know their child's diagnosis. Among those who did, the caregivers' depression was compared across different diagnosis groups. The caregivers of children with ADHD were most depressed (M=19.82, SD = 8.60), followed by caregivers of children with autism (M = 17. 41, SD = 9.34), developmental delays (M= 15.40, SD = 6.99), intellectual delays (M = 15.83, SD = 8.41) and language delays (M = 13.08, SD = 10.28), although there is no significant difference among the four groups, F (4, 62) = .96, $p>.05$. Among the caregivers whose children were diagnosed with ADHD, 8 out of 11 scored beyond the cut-off point of 16 (72.7%), while 12 out of 17 caregivers whose children were diagnosed with autism scored above 16 (58.7%). Among those caregivers whose children were diagnosed with developmental delays, 7 out of 15 scored above 16 (46.7%). Among those whose children were diagnosed with intellectual delays, 4 out of 12 (33.2%) scored above 16, and of those whose children were diagnosed with language delays, 4 out of 12 (33.2%) scored above 16. For a significant proportion of the caregivers of children with ADHD and autism, the long-term demands of caregiving appear to have severely affected their mood.

c) Social Support and Depression

It was hypothesized that the caregivers who received higher levels of social support would be less depressed. The intercorrelations between the variables were computed by conducting Pearson Product Moment Correlations and are presented in Table 3. There was no significant correlation between the total scores for informal support based on SSSCDD and the total scores for depression based on CESD, r (106) = -.13, $p>.05$. There was no significant correlation between the total scores for professional support based on SSSCDD and the total scores for depression based on CESD, r (106) = -.12, $p>.05$. The amount of informal and professional support, which was measured by assessing the number of people who were available to provide support, was not significantly related to the caregivers' experience of depression. There was a significant correlation between the total scores for perceived support based on MSPSS and the total scores for depression based CESD (r (107) = -.31, $p<.001$), suggesting that the caregivers who perceived a lower level of social support experienced a higher level of depression.

d) Correlations among psychosocial, child and demographic variables

The intercorrelations between the demographic, child and psychosocial variables were computed to examine the relationships between psychosocial variables and child and demographic variables (Table 3). Caregivers' depression was significantly related to the child's maladaptive behavior, family socioeconomic status and mother's education. Caregivers who had children with more maladaptive behaviors experienced a higher level of depression than those whose children exhibited fewer maladaptive behaviors, r (106) = -.31, $p<.001$. The caregivers experienced elevated depression when their families had a lower socioeconomic status (r (107) = -.20, $p< .05$) and when the children's mothers were less educated, r (107) = -.19, $p<.05$.

Caregivers were more likely to perceive a higher level of social support when their children were younger (r (107) = -.23, $p<.05$), the mother had obtained a higher level of education (r (107) = .20, $p<.05$), and the family had a higher socioeconomic status, r (107) = .19, $p <.05$. However, the perceived social support was not related to the adaptive or maladaptive status of the children. Neither the amount of informal support nor that of professional support was related to child's adaptive and maladaptive functioning, mother's education, or socioeconomic status of the family.

e) Predictors of depression among caregivers

The four variables that correlated significantly with depression (child's maladaptive behavior, mother's education, socioeconomic status, and perceived social support) were entered into a hierarchical regression analysis to determine the best set of predictors of depression among caregivers (Table 4). The first step included the child's maladaptive behavior as a stressor. The other variables (mother's education, socioeconomic status and perceived social support) were entered into the regression as family resources to determine if they entered significantly in a second step of the hierarchical regression. Table 3 shows the four variables that were entered into two steps. The first predictor variable accounted for nearly 10% of the variance in depression scores (F (1, 107) = 11.48, $p < .001$). Child's maladaptive behavior accounted for a significant amount of the variance in depression among caregivers. Mother's education, socioeconomic status, and

perceived social support also entered the model significantly, accounting for an additional 8% of the variance in stress scores (F (4, 104) = 5.53, $p < .001$). When all four independent variables were included in the second step, neither socioeconomic status nor maternal education was a significant predictor of depression. The most important and significant predictor of caregivers' depression was perceived social support followed by child's maladaptive behavior.

V. Discussion

The present study explored the linkage between depression and social support among the caregivers of young children with developmental delays in Vietnam. The level of depression experienced by Vietnamese caregivers of children with developmental delays was affected by their perceived social support. The more the caregivers felt that they received support, especially from family, friends or somebody special, the less depression they experienced. This finding is consistent with those of previous research on the relationship between social support and depression [22,23]. However, when social support was measured in terms of the amount of support available to the caregivers, neither informal nor professional support had a significant impact on depression, implying that the mere number of people available does not significantly affect the caregivers' mood. Only when the caregivers really felt that they were cared for did the amount of social support show a significant relationship to mood.

The extent of maladaptive behavior had a significant impact on depression among the caregivers. The impact of maladaptive behavior of the children on the stress levels and mood of the caregivers has been consistently documented in many of the previous studies [5,22–24]. Beyond and above the intellectual and adaptive challenges their children bring to the caregiving, when the children show impulsive, aggressive or unruly behaviors, this has a significant influence on the mood of the caregivers, suggesting that the demands of coping with the children's maladaptive behaviors have a long-term impact on the quality of the everyday mood they experience.

In addition, the level of the caregivers' depression in Vietnam is alarming, with more than half of them scoring at a level consistent with clinical depression. Although the ways in which depressive symptoms are expressed can vary from culture to culture, many Vietnamese caregivers appear to suffer far more severely than those in Western culture: The prevalence rate of depression has been reported at 20% to 30% among US mothers of children with intellectual disabilities [5,22,25]. In particular, a significant proportion of Vietnamese caregivers of children with ADHD (72.7%) and autism (58.71%) suffer from this suspected clinical level of depression, revealing that children with behavioral problems impose long-term demanding caregiving burdens to such an extent that their caregivers' mood deteriorates. Depression, especially at clinical levels, is about losing a sense of meaning and motivation in everyday life. The impact on the caregivers was such that coping with their children was not just overwhelming and difficult, but they felt that there was no hope and fun in their lives, only the interminable sadness, helplessness, hopelessness and exhaustion of coping with their difficult children and not getting

Table 3: Correlations among variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12
1. Age												
2. Child's Gender	0.08											
3. Mother's Education	-0.18	0.05										
4. Father's Education	-0.06	0.05	0.71**									
5. Economic Status of the family	-0.12	0.21	0.32**	0.00								
6. Perceived Social Support	-0.23	0.06	0.20*	0.28	0.19*							
7. Parent Depression	0.07	0.01	-0.19*	0.16	-0.20*	-0.31**						
8. Social Support Informal	-0.02	-0.05	-0.01	0.87	0.00	0.19*	-0.13					
9. Social Support Professional Total	0.00	-0.08	-0.10	0.53	0.15	0.12	-0.12	0.32**				
10. Social Support Total	-0.01	-0.07	-0.04	0.73	0.05	0.20*	-0.14	0.94**	0.62**			
11. Parent Mental Health	0.00	0.07	-0.20*	0.07	-0.26**	-0.11	0.53**	0.05	0.02	0.05		
12. Child Functioning Weighted Score	0.40**	-0.10	0.13	0.53	-0.20*	0.08	-0.15	0.14	0.18	0.19	0.01	
13. General Maladaptive Index	-0.22	-0.03	0.25**	0.46	0.28**	0.12	-0.31**	-0.13	-0.08	-0.14	-0.30**	-0.14

*Note. *p < .05; **p < .01; two-tailed tests*

Table 4: Regression model: Predictor Variables of Depression (n = 109)

Independent variable	*B*	*SE*	*Standardized B*		*F*	R^2 Change
Step 1					11.48	0.10***
Child's maladaptive behavior	-0.35	0.10	-0.31	***		
Step 2					5.53	0.08*
Child's maladaptive behavior	-0.26	0.11	-0.24	**		
Family SES	-1.39	2.08	-0.07			
Mother's education	-0.60	0.98	0.06			
Perceived social support	-0.44	0.16	-0.25	**		

*Note. *p< .05; **p< .01; ***p < .001; two-tailed tests.*

the support they needed. These were caregivers of young children: When the caregivers' daily mood is affected this severely when their children are young, we can only imagine how they will fare as their children advance in age without having their behavior issues addressed. It is paramount that the caregivers of children with behavioral issues obtain support to manage the daily issues arising from their children's maladaptive behaviors.

When we examined the availability of informal support, we found that caregivers mostly relied on their spouses for help as well as on both the mothers' and fathers' parents. Although the availability of informal support was not related to depression, it was related to perceived support. Having a large enough number of people around to provide support to the caregivers could be helpful in their perception of social support, which in turn might help with the depressive symptoms. Regarding professional support, almost all caregivers (91.7%) reported the availability of private therapists. These therapists could be professional therapists, but in an attempt to advance their children to an upper level in school (the kindergarten programs in Vietnam hold the children to repeat the grade until they are qualified to advance to elementary schools), they tended to hire many private tutors, who were often college or high school students without training in special needs, to help their children to master academic materials. This could be a costly and inadequate investment: The children with cognitive and attention issues might resent having to work on demanding academic materials just to move on to the advanced level. A quarter of the caregivers (27.5%) reported that teachers were available, which is disappointing considering that all these children were enrolled in kindergarten programs. It is clear that many teachers do not have enough skills to work with these children. There should be more formal training programs available to train the teachers to work with the children with special needs in integrated and inclusive settings of kindergarten programs in Vietnam. While many caregivers are severely affected by their children's condition, especially when they have behavioral issues, there should be more professional support systems that could train and provide teachers who could address these issues.

Mother's education was significantly related to depression and perceived social support. When the mothers were more educated, the caregivers experienced less depression and perceived a higher level of social support. When mothers are highly educated, they tend to attain higher socioeconomic status, enabling them to utilize the greater financial resources to better care for their children. In addition, they have more intellectual resources, which can enable them to develop better strategies to cope with the children's demanding cognitive and behavioral issues and thus to experience less depression. They may be able to make more effective use of the available social support in raising their children. While general support services should be available to all the families, there should be more support and education available for the mothers with less education and financial resources. Helping mothers to build and strengthen coping strategies and informal support systems could be critical for the well-being of the caregivers, and this needs to be addressed when the programs for young children provide the services. The findings also suggest that there is a need for services and supports that help caregivers not only to be effective parents, but also that address feelings of distress that stem from parenting children with disabilities. This support needs to come from professionals who can provide mental health counseling or psychotherapy, helping the caregivers develop effective personal coping strategies.

The study has a few limitations. Our project was geographically limited to Hanoi, the capital city and one of the biggest cities in Vietnam. Most of our participants were relatively well educated and the majority had completed their college degrees. In addition, although developing, the resources for children with special needs are relatively concentrated in big cities like Hanoi, where the families could rely on professional help to take care of their children more than could those residing in smaller cities or countries. We suspect that

parents with less education and with fewer financial resources in other areas of Vietnam are in a direr situation in coping with the issues their children impose on them.

As in many other Asian cultures, negative perceptions and attitudes prevail in Vietnam toward individuals with disabilities. These perceptions and attitudes are often extended to their caregivers and families, who may be perceived as not raising their children properly [10,11]. While there should be environmental support for changing the attitudes toward those with disabilities, the experience of stigma should be explored in future studies as impacting the caregivers' mood and diminishing the quality of life that individuals with disabilities and their families deserve.

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By Shweta Kanchan, Sunita Tiwari & Shweta Singh

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Keywords: cognitive behavior therapy (CBT), pittsburgh sleepiness scale (PSQI), epworth sleepiness scale (ESS), dim light melatonin onset (DLMO).

GJMR-A Classification: NLMC Code: WM 165

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I. Introduction

The present study was conducted to find out the efficacy of cognitive behaviour therapy on different sleep parameters and circadian phase timings in college students in the age group of 18 to 25 years. Young college going adults are more prone to delay their sleep and report poor sleep quality because of the demand of career and social life in a highly competitive environment . Several previous studies have shown that adequate quantity and quality of sleep is required for optimal physiological functions (1). Young adults suffer from several short term and long term consequences due to sleep lack in the form of excessive daytime sleepiness, irritability, cognitive impairment, depression, low immunity, metabolic disorders (2). The present study tries to understand the effects of cognitive behaviour therapy in improving their sleep parameters and circadian phase advancement.

Author α: e-mail: drshwetakanchan@gmail.com

II. Methodology

The present study was conducted on students of MBBS and BDS in King George's Medical University, Lucknow. A screening questionnaire based on Pittsburgh Sleep Quality Index (PSQI) (3) was served initially, this questionnaire gives information about the sleep quality and from all those who scored more than 7 on the PSQI and consented to participate, subjects were randomly selected using random number table and finally 50 subjects were recruited for the study. The participants selected were given epworth sleepiness scale to find out the degree of daytime sleepiness. A score more than 10 in the epworth sleepiness scale (ESS) (4) indicates significant degree of daytime sleepiness. The subjects were provided with sleep diaries which had to be filled for 14 days after which an overnight polysomnographic study of subject was conducted using SOMNOscreen plus EEG32 video equipped polysomnography with a resolution of 16 bit, sampling rate up to 512 Hz, and band pass filter of 0.1 to 128 Hz. Standard electrode placement for EEG(f4-m1, c4-m1, o2-m1 along with alternate at f1-m2, c1-m2,o1-m2), chin EMG and other channels according to the recommendations of the AASM were used. Parameters which were considered for the study were sleep latency (SL), sleep efficiency, REM latency, Total Sleep Time(TST). Changes in sleep architecture using the above parameters before and after intervention was compared. Along with the polysomnography circadian rhythm was marked by their salivary melatonin level by collecting salivary samples every 30 min beginning at 9:00 pm till the subject goes to sleep , both sleep study and salivary collection were conducted in the sleep lab on the same night. Subjects were expected to collect saliva in labeled eppendorf tubes, collection was conducted in the sitting position in dim light of less than 30 lux (5), the subjects were refrained to eat in the lab, about 4 to 5 ml of saliva was collected and promptly refrigerated, early in the morning salivary samples were centrifuged at 2000 RPM and the and the supernatant was stored at minus 80 degree and examined when all samples were collected. Human melatonin Elisa kit from Bioassay technology laboratory was used for salivary melatonin estimation, Elisa test was conducted according to the user instruction, a standard curve

plotting the optical density of each sample and was corellated with salivary melatonin concentration. The Dim light melatonin onset (DLMO) is the time at which the salivary melatonin reached 4pg/ml, it is considered a useful parameter for estimation of circadian rhythm (6), DLMO time was noted. After completing all sessions of cognitive behavior therapy (CBT), a sleep study was again conducted accompanied with salivary melatonin estimation for circadian phase change using DLMO as a marker was noted. The subjects were given intervention in the form of cognitive behaviour therapy in 4 to 5 session. Cognitive behaviour therapy module were prepared according to the sleep related complains faced by these young students obtained after interviewing them. These models were divided into four weekly sessions of 45 minutes to 1 hour each a fifth session was administered if needed. They were given a sleep diary after the completion of all CBT sessions, while they were expected to comply with the instructions and methods learned during CBT. A morningness eveningness questionnaire was also served both before and after the intervention to find out any changes in the chronotype, PSQI scale and the Epworth Sleepiness Scale, were also served after completion of the study.

III. Results

The present study showed that the mean Pittsburgh sleep quality index and the Epworth sleepiness scale slightly decreased post intervention though the changes were not statistically significant (table 1). The total sleep time increased significantly by a mean of 26.43 minutes from the sleep time prior to the intervention. sleep latency however the difference was not statistically significant from 14.70 min before intervention to 13.94 min post intervention. Sleep efficiency showed slight improvement from 89.76% to 92.66%, the changes were more in males than females. REM sleep latency decreased from 123.98 to 109.40 min the mean bed time change was an advance of 123.16 min and the wake up time did not change much, mean wake up time change was 14 min for the participants and remain somewhere between 7 to 7:30 a.m. because the wake up time was mostly decided by their college schedule and they did not have much choice (table 1). The changes in different parameters were nearly same for both the genders however males showed more significant increase in sleep efficiency compared to females (table 2) The dim light melatonin onset (DLMO) advanced by nearly 42minutes leading to a circadian phase advancement in the post intervention assessment (figure1). The chronotype type as assessed by MEQ score showed no change in the percentage of subjects with a morningness chronotype (18%), however the subject with intermediate chronotype increased slightly from 74% to 76%(table 3).

IV. Discussions

The present study reiterated the findings to several previous study which have found cognitive behaviour therapy to be an effective intervention in advancing phase and also improving sleep quality in young adults. A previous study by Yu jen lee, et all (7) showed that poor academic performance is associated with sleep debt and is represented by extended weekend sleep in case of young college going adults. In the Present study most of the participants had impaired night time sleep in form of less duration of sleep and a poor quality sleep, extended sleep on the weekends along with that they had in poor daytime performance reflected by high scores on the ESS scale, because of insufficient sleep. Most of the participants fulfilled the criteria of behavioral induce insufficient sleep syndrome. Insufficient sleep syndrome has an undiagnosed burden on the gross domestic product and looking at this it has been demanded to declare insufficient sleep a public health epidemic Vijay chatta(8). A study by Stephen Baker(9) the prevalence of mental health problems in college students could link some of the problems to poor sleep the present study also found a very high degree of daytime sleepiness in college students which could be because of the sleep debt that they carry over months, this chronic sleep insufficiency could lead to delayed sleep phase disorder and other health related complains in the long run and should be timely addressed (10). A previous study conducted by Michael Gradiser(11) on the effect of CBT and bright light for the treatment of delayed sleep phase disorder in adolescence showed that CBT is an effective intervention for improving multiple related problems and daytime impairment.

Another study by Zong Rui Ma(12) cognitive behaviour therapy in children and adolescents with insomnia a significant pooled effect size was observed for sleep onset latency and sleep efficiency there was no effect on the wake after sleep onset and other parameters .The present study also observed changes in sleep latency and sleep efficiency after cognitive behavior therapy. Bei Bei et all (13) showed the chronotype in sleep efficiency is associated with sleep outcome the of cognitive behaviour therapy this could explain why the students shift a little from eveningness to intermediate chronotype after the intervention. Melatonin is a very important physiological measure of circadian phase it is not just feasible but also very easy to measure compared to plasma melatonin or urinary melatonin, Henry keijer (14) showed that salivary melatonin is effective measurement of DLMO correlates well with plasma melatonin and urinary melatonin levels. The study used salivary melatonin as a marker of circadian phase.

V. Conclusion

The presence of poor sleep quality and quantity in young adults can lead to poor health in the long run. Cognitive behavior therapy has shown effectiveness in improving sleep and circadian parameters in young adults, it should be encouraged as an effective non pharmacological therapy for better sleep with stress on improving sleep hygine and promoting awareness towards better sleep in the community.

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Table 1: Descriptive Statistics of All Variables

	N	N=50		
		Mean	Median	SD
AGE Years	50	20.26	20.00	1.90
TIME SPEND IN INSTT.(months)	50	5.50	4.00	2.82
BMI	50	22.34	22.03	2.74
PSQI-Pre	50	11.56	11.50	1.86
PSQI-Post	50	11.40	11.00	1.92
ESS-Pre	50	8.90	9.00	1.57
ESS-Post	50	8.60	9.00	1.73
TST-Pre	50	297.94	300.00	22.90
TST-Post	50	324.22	325.50	23.06

TST-Pre	50	4.97	5.00	0.38
TST-Post	50	5.40	5.43	0.38
SLEEP LATENCY-Pre	50	14.70	14.50	5.25
SLEEP LATENCY -Post	50	13.94	14.00	5.45
%Sleep efficiency-Pre	50	89.76	89.50	3.30
%Sleep Efficiency-Post	50	92.66	94.00	3.46
REM Latency-Pre	50	123.98	127.00	14.73
REM Latency-Post	50	109.40	110.00	15.04
BedTime Change	50	123.16	120.00	33.64
WakeUpTime Change	50	14.00	15.00	14.03
DLMO Time Change	50	-42.00	-40.00	26.42

Table 2: Gender Wise Summary of Different Parameters

	Sex	M	F
	N	21	29
PQSI-Change	mean	0	-0.27586
	sd	3.11448	2.34363
	p	1	0.5312
	N	29	21
ESS-Change	Mean	0.45	0.10
	SD	2.37	2.59
	p	0.1582	0.8667
TST-Change	Mean	26.17	26.43
	SD	17.89	15.55
	p	<0.00001	<0.00001
Sleep Latency-	Mean	-0.34	-1.33
Change	SD	4.34	4.18
	p	0.6705	0.16
%Sl.Efficiency	Mean	3.24	2.43
	SD	2.86	3.53
	p	<0.00001	0.01
REM-Change	Mean	-14.21	-15.10
	SD	7.04	5.53
	p	<0.00001	<0.00001
DLMO CHANGE	MEAN	-41.38	-36.92
	SD	18.46	24.66
	P	<.0001	<.0001

Table 3: Morningness-Eveningness Scores (Meq Scores) Pre and Post Cbt Intervention

EQ SCORE	N=50		N=50	
	Pre(number)	percentage	Post(number)	percentage
Morningness	9	18%	9	18%
Eveningness	4	8%	3	6%
Intermediate	37	74%	38	76%

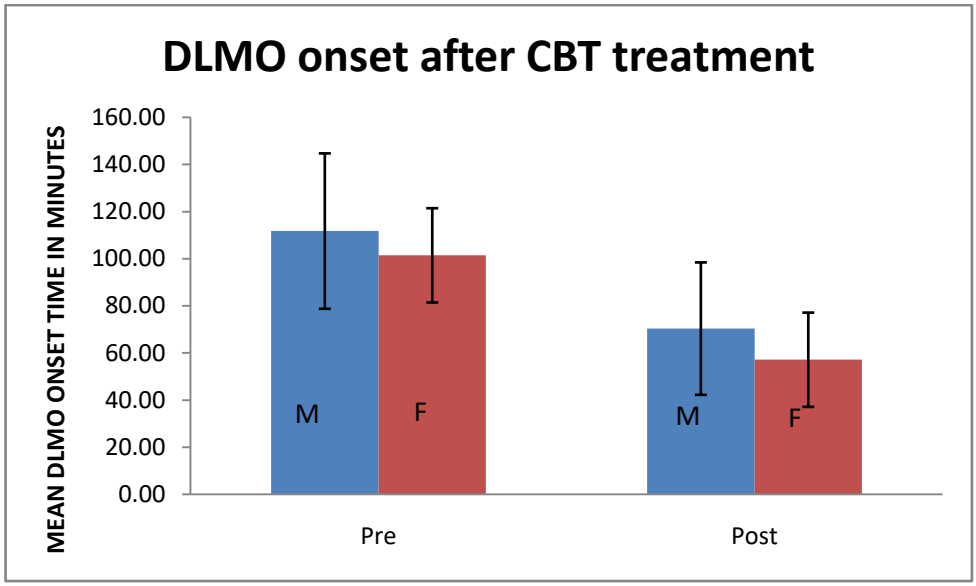

Figure 1: Mean Dlmo Onset Time in Minutes dor Males Vs Females Before and after Intervention

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Correlation of EEG Envelopes is the Best Method for Identifying Mental Diseases, Functional States, Individual and Intergroup Differences

By Alexey Pavlovich Kulaichev

Lomonosov Moscow State University

Abstract- The principal errors of spectral and coherent analysis are discussed, and the mathematics of these methods is not related to EEG nature. In this regard, in 2011, the new method was developed for evaluating EEG synchrony by the correlation of envelopes, which has a direct and fundamental physiological meaning. The basics of this method and the methodology of subsequent multilateral statistical analysis are considered. The effective use of the method for identifying individual and intergroup differences in the norm and several types of schizophrenia, depressive diseases, five stages of sleep, and similar functional states are presented.

Keywords: EEG, metrology, amplitude and power spectra, coherency, envelope, correlation, statistical analysis, schizophrenia, depression, sleep stages, functional states.

GJMR-A Classification: NLMC Code: WL 141

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Keywords: EEG, metrology, amplitude and power spectra, coherency, envelope, correlation, statistical analysis, schizophrenia, depression, sleep stages, functional states.

I. Introduction

Unfortunately, in the field of computational or quantitative EEG (qEEG), metrological criteria, assessments and standards have not been formed globally for several of reasons [1]. As evidenced by the content of the special fundamental monograph [2] and many journal publications on qEEG, metrological issues almost do not attract the attention of EEG researchers. The new proposed mathematical methods are not compared with analogs; their effectiveness in solving typical physiological problems is not evaluated, is not compared and is not statistically verified. Traditional methods are not critically examined and rethought. Periodically, attempts are made to introduce completely exotic and unrelated brain physiology methods from the theories of chaos, information, and entropy, fractals, attractors, automatic regulation, nonlinear dynamics, wavelets, etc.

One way or another, but scientific research of EEG mainly followed in the wake of physical and technical applications of mathematical methods of signal analysis which were often directly and uncritically transferred by involved engineering and physical specialists without due consideration of a) the fundamental non-stationarity of biosignals; b) the inharmonic nature of their sources; c) the presence of amplitude modulation. Indeed, there is not a single well-known a pure or applied mathematician who has contributed to the development of special methods of EEG analysis. As a result, many methods that were inadequate in this field were transferred, which, in the absence of metrological criticism, leads to incompatibility and inconsistency of the results and conclusions obtained by different researchers. And such a situation can in no way be recognized as the scientific one.

It is no exaggeration to say that the main means of qEEG are [2] spectral estimates of EEG amplitude in frequency domains and estimates of synchrony between pairs of derivations using the coherence function.

II. EEG Amplitude Estimates

During the pre-computer era, EEG amplitude was estimated by direct measurements (DM) of EEG waves. After the FFT algorithm appearance in 1965, EEG amplitude was indirectly estimated (IdE) from the amplitude and power spectra. There is no doubt that DM acts as an indisputable standard, and IdM may differ from them in the resulting values. The corresponding comparison was carried out in the special metrological study [3], and it showed the following differences:

1) The three studied in [3] DM indicators give almost equivalent estimates that highly significantly differ from IdE;
2) DM demonstrate the smooth dynamics of their value change at successive epochs, whereas IdE are subject to drastic and casual fluctuations;
3) IdE, unlike DM, don't possess the property of additivity, which is inherent for statistical averaging, its values depending on the number and length of averaged epochs can differ in 3 or more times;
4) IdE on simulated signals with known amplitude ratio give estimates by 1.4–1.55 times different from true value whereas DM proper correlations of average amplitudes;
5) IdE depending on the shape of spectrum amplitude distribution, may vary in its ratio to a variety of subjects more than five times while DM show the

Author: Lomonosov Moscow State University, Biology Department, Russian Federation. e-mail: akula-@mail.ru

same relation of values which differ from IdE in 1.38–3.7 times;

6) The largest errors were found for the power spectrum.

These conclusions do not allow metrologically qualify IdE as the analytical tools adequate to the nature and specifics of EEG potentials. Their use may lead to the incompatibility of results obtained by different researchers.

In addition, the spectra have an extremely distant relation to EEG nature since, unlike sound and electromagnetic signals, EEG is not the sum of harmonics. EEG is the sum of postsynaptic potentials under the electrode whose short-time changes take the form of asymmetric bell-shaped functions. Therefore, individual spectral harmonics have no physiological meaning. They change arbitrarily both when the length of the analysis epoch changes, as well as on neighboring epochs.

III. Coherence

The poorly known history of EEG coherence is a vivid example of the mass spread of pseudoscientific misconception. The coherence function was formulated in 1930 by Norbert Wiener [4], implementing the idea previously expressed by David Hilbert that it would be good to have something similar to Pearson correlation in the spectral region. Wiener intended this function for problems of quantum mechanics and nonlinear optics, which are obviously extremely far from EEG studies. Subsequently, coherence became widespread in the analysis of physical signals but as a purely auxiliary indicator for assessing the significance of other cross-spectral characteristics [5].

Many years have passed when in 1963, the newly minted young Ph.D. [6], without any reference to sources and predecessors, proposed coherence as the main indicator of EEG synchrony. This Ph.D. published 2–3 more articles on this topic, after which he lost interest in it. But the growing snowball of coherency rolled around the world, capturing the minds of many thousands of followers like a mass pandemic.

The special metrological analysis of the weaknesses and errors of coherence was carried out in the study [7], which gave the following results:

1) The coherence mainly evaluates the degree of phase instability of the cross-spectrum of two EEG signals, which to an even greater extent than spectral harmonics has no physiological meaning;
2) At the same time, the coherence also changes depending on the ratio of the values of the cross-spectrum vectors at neighboring epochs[1], and such a dual sensitivity is unacceptable for a measuring instrument;
3) The coherence dependence on phase instability has a highly nonlinear snake-like character, which is unacceptable for accurate measurements;
4) The coherence values are strongly influenced by choice of four setting parameters which is also unacceptable for a measuring instrument;
5) Different EEG analyzers secretly use different settings of these parameters, so the obtained coherence values are incompatible.

Thus, coherence evaluates unknown what, unknown how, and unknown why, being an example of pseudoscientific anachronism. As the literature reviews, performed in the three main areas of scientific and medical research, show [9–11], the use of coherence leads to a total incompatibility of results on the localization of inter-individual and intergroup differences. Thus these numerous publications do not belong to the field of science, which is designed to search for and finds objective laws in natural phenomena, but to the category of random noise or pseudoscientific garbage.

IV. Correlation of EEG Envelopes

In connection with the numerous and fundamental errors of coherence considered, another and adequate assessment of EEG synchrony was proposed in 2011 [8] by calculating the Pearson correlation coefficient between the envelopes of two EEG derivations. Unlike coherence, this assessment has a direct and fundamental physiological meaning. Indeed, since the envelope represents a change in EEG amplitude modulation (fig. 1)[2], it increases with increasing synchrony in the change of postsynaptic potentials under the electrode. Therefore, the envelopes correlation evaluates the degree of synchrony in the dynamics of postsynaptic synchrony between two EEG derivations.

[1] As the difference in values of vectors increases, the coherence increases, which is directly opposite to the Pearson correlation property. Thus, Wiener, in his algorithm, distorted Hilbert's original idea.

[2] Mathematically, the envelope is a module of an analytical (complex-valued) signal, the real part of which is equal to the signal itself, and the imaginary part is obtained from the signal by the Hilbert transform. In turn, Hilbert transform is equivalent to the double Fourier transform, when before the reverse transformation, all spectral harmonics are shifted in phase by 90°.

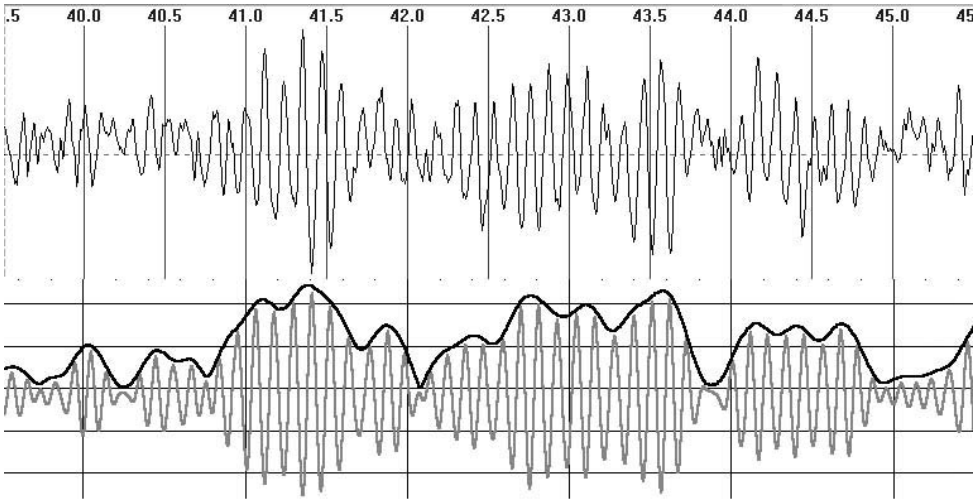

Fig. 1: Example of an envelope: *above* – EEG with a high content of alpha rhythm; *below* – the result of filtering in alpha domain[3] with an overlay of the envelope.

It was found that in more than 42% of cases, there are high correlations between the envelopes of closely located (neighboring) derivations from 0.6 to 0.99 at the median = 0.42, while for more distant derivations, 98.5% of the envelope correlations do not exceed 0.6 at the median = 0.17. At the same time, highly correlated connections between the envelopes form distinct topographic patterns on the scalp, which are largely preserved in neighboring EEG frequency domains.

This allows us to reduce the amount of significant information, limiting ourselves only to the grid of connections between nearby pairs of derivations; for the 10–20% scheme, such pairs will be 43 (Fig. 2, a). The use of such a standard grid, in particular, contributes to the comparability of the results obtained by different researchers. Within the framework of such a grid, it is easy to visualize highly correlated connections between envelopes (Fig. 2, *a*–*c*), obtaining well-visually detectable topographic patterns.

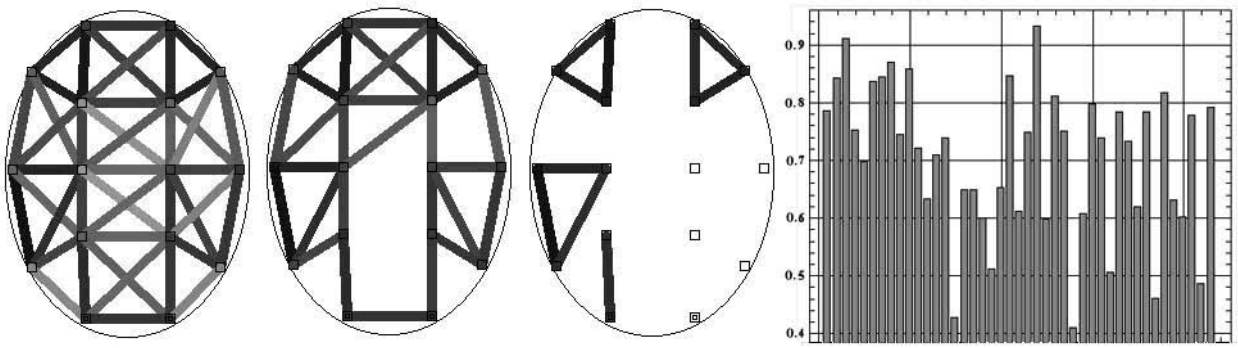

Fig. 2: The three topogramms of EEG synchrony of chosen subject for standard grid of channels depending on correlation value r_{xy}: *a* — r_{xy}>0.2; *b* — r_{xy}>0.6; *c* — r_{xy}>0.8; *d* — profile of synchrony for chosen subject: *vertical axis* — correlation values; *horizontal axis* — the nearby pairs of derivations ordered from left to right and from top to down according to its arrangement on a scalp.

[3] Preliminary filtering of the signal in the selected frequency domain is preferably performed by the double FFT method, characterized by minimal amplitude and phase distortions compared to classical filters.

The sequence of correlation coefficients between EEG envelopes for pairs of derivations in their ordered sequence in such a standard grid is called the profile of synchrony (PS) of the subject. It is convenient to depict PS in the form of a bar chart (Fig. 2, d), which provides the researcher with an additional visual pattern. It is precisely such profiles that are the source material for the further areas of analysis.

In the case of a group of subjects, we will have a PS matrix (Fig. 3): columns are pairs of derivations from the standard grid, rows are the subjects. Such matrices can be obtained: 1) for different time intervals of the same functional state; 2) for different functional states; 3) for different frequency ranges; 4) for different groups of subjects that differ in certain characteristics, etc. And such matrices in further directions of analysis can be compared in pairs (Fig. 3): 1) by the same pairs of derivations (by columns); 2) by the same subjects (by rows); 3) for all subjects, each with each; 4) for pairs of derivations each with each.

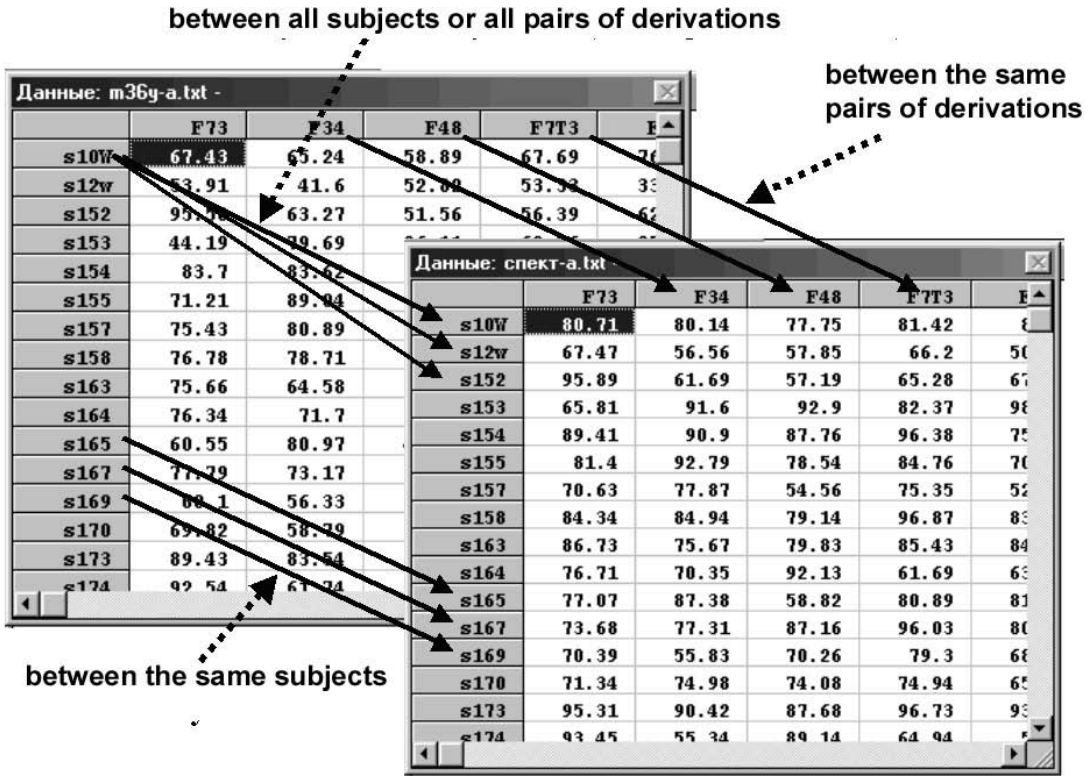

Fig. 3: The example of two matrices with profiles of synchrony for two groups of subjects and three variants of its comparison.

V. Methodology of the Subsequent Analysis

After calculating PS of two or more groups of subjects, it is necessary to identify and reliably statistically justify the existence of differences of interest to the researcher [8]. For individual pairwise comparisons, there are several options (Fig. 3). The similarity of the compared pairs is estimated by the correlation coefficients of Pearson, Spearman, Kendell, etc., and the differences are estimated by the parametric and nonparametric criteria of Student, Fisher, Wilcoxon, signs, Ansari Bradley, Klotz, Kolmogorov–Smirnov, etc. Thus, it is possible to identify completely different PS patterns characteristic of *pathology* and *norm* groups (Fig. 4). Simultaneously, it should be remembered that with several paired comparisons at the same time, it is necessary to adjust the critical level of significance of null hypotheses using the Bonferroni correction.

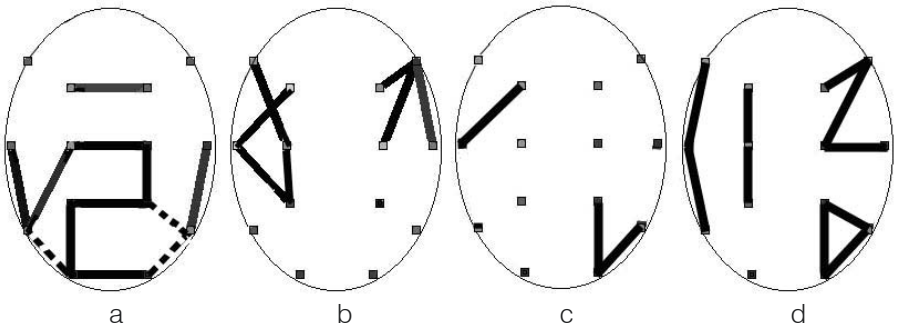

Fig. 4: Differences in EEG synchrony of alpha domain among two groups of examinees: *a* — the differences between pairs of EEG-channels on significance level $p<0.05$ (solid lines — more EEG-synchrony in the *norm* group, dotted lines — more EEG-synchrony in the *schizophrenia* group); *b* — statistically undistinguished pairs of EEG-channels on significance level $p>0.6$; *c* — the differences between symmetric pairs of EEG channels (dominating pairs are shown) in *norm* group; *d* — the differences between symmetric pairs of EEG-channels in the *schizophrenia* group.

Further, it is possible to study the difference and similarity of PS of each subject in different frequency domains and at different time intervals to assess the stability of the functional state. Here, according to the correlation coefficients r_{jj} between PS of each *j*-th subject in two adjacent frequency domains or on neighboring time intervals (Fig. 3), it is possible to make inter-individual comparisons and ranking of the subjects.

The next direction is the use of multidimensional statistical methods to identify intergroup differences. The differences of the matrices in the average PS values are estimated using the 2-ways ANOVA method.

The next step may be to use factor analysis for each matrix to identify PS, mainly projected on the principal factor axes. As follows from Fig. 5, these projections are fundamentally different for the *norm* and *pathology* groups. To quantify the differences, it is possible to calculate correlations between the factor loadings of PS for each factor performed between the two groups of subjects. As a result, the correlations for the three principal factors are obtained at a minimum of 0.106–0.328, which indicates a fundamental difference in factor structures and intergroup differences.

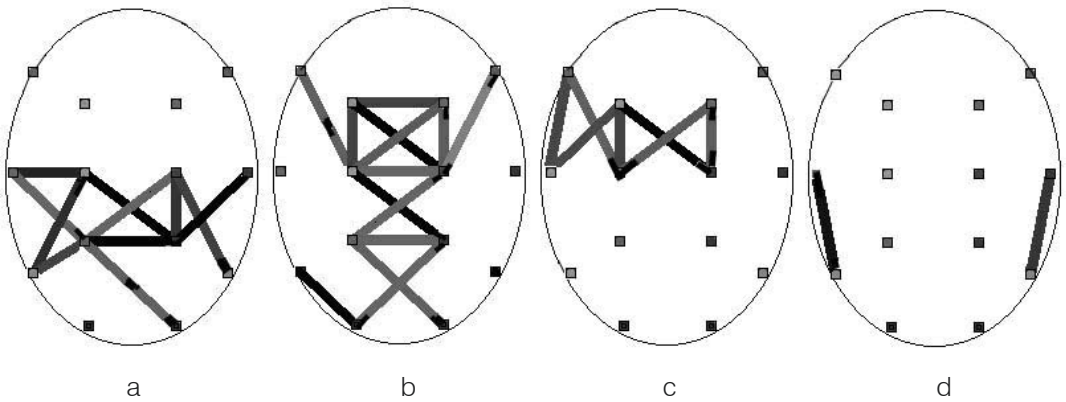

Fig. 5: The pairs of EEG derivations which PS has preferential projections on the first (*a, b*) and second (*c, d*) of main factors for the *norm* (a, *c*) and *schizophrenia* (*b, d*) groups.

One of the most important methods is to use the discriminant analysis, which allows us to construct a classifying function for a statistically reliable and stable division of subjects into two analyzed groups. Such a function can be practically used to assign new individuals to a particular group, that is, as a means of preliminary medical or functional diagnostics.

VI. Identification of Highly Consistency Groups of Subjects

One of the important statistical tasks is the identification and processing of outliers and the selection of homogeneous groups of subjects, which, unfortunately, are almost not taken into account in EEG studies. Such outliers are the result of the action of

extraneous and accidental causes that can mask really existing patterns. Inattention to these issues may lead to the identification of *pseudo-significant* or *pseudo-not-significant* individual and intergroup differences.

Since in the method under consideration, we do not have samples of variable values, but PS are the sets of measurements, so we do not apply the usual method of detecting outliers by large deviations from the average value. Therefore, a special method of averaged correlations of PS was developed [8]. In this case, for each group, paired correlations r_{jk} between PS of all *j,k*-subjects are calculated at a given time interval. Then we get a square correlation matrix $|r_{jk}|$ by which the average value $M_j(r_{jk})$ from its correlation with all other *k*-th subjects is determined for each *j*-th subject. Then, using the obtained $M_j(r_{jk})$, variation series or Quetelet graphs are constructed (Fig. 6), on which subjects with low consistency or outliers are distinguished. They may be the result of uncontrolled features of current functional and mental state or errors in diagnosis. Therefore, they should be removed from further analysis.

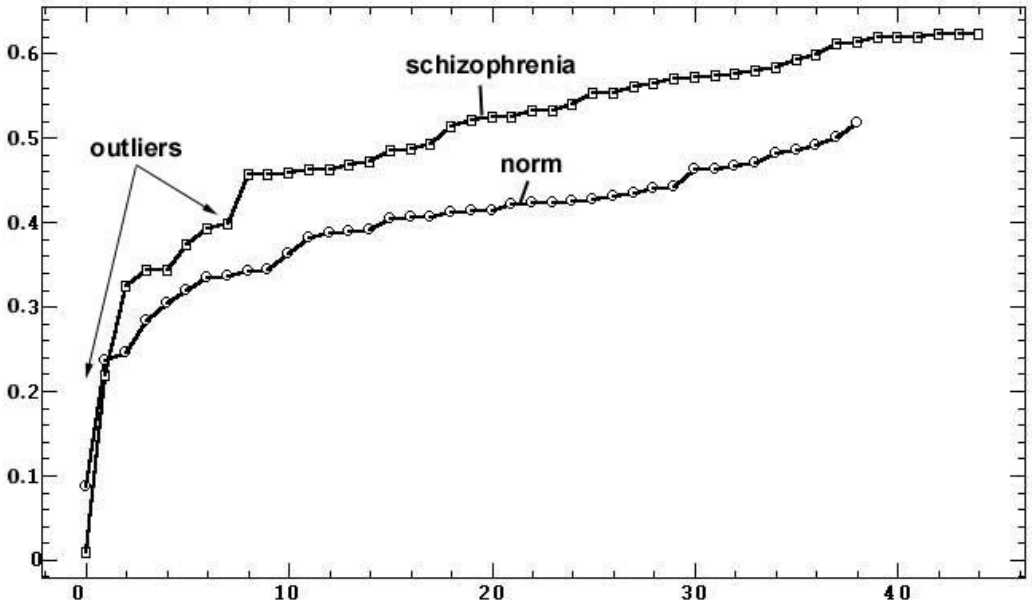

Fig. 6: The diagram of the distribution of average correlation between PS of alpha domain in two groups of subjects: *vertical axis* — correlation values; *horizontal axis* — the subjects ordered on increase of average correlation.

Fig. 6 also shows a higher value of average consistency in *pathology* group $M_j(r_{jk})=0.505\pm0.12$ in comparison with *norm* group $M_j(r_{jk})=0.397\pm0.084$ with their significant difference at the significance level $p<0.00005$. This confirms a well-known rule: «*every healthy person is healthy in his own way, but all the "sick" persons are sick in the same way*». This is a real confirmation of the effectiveness and adequacy of the envelope correlations method.

VII. Results of the Method Application

The described method of envelope correlations (MEC) was used to assess various mental diseases and functional states. EEG recordings were carried out in a state of relaxation with closed eyes according to 10–20% system of derivations.

a) Schizophrenia [8]

The material included adolescents aged 10–14 years: 39 schoolchildren without mental disorders (the control or *norm* group) and 45 patients with schizophrenic disorders in categories F20, F21, F25 according to ICD-10.

The following significant results were obtained: 1) numerous topographic patterns that are far from a random distribution (Fig. 2, 5); 2) proximity of topographic patterns in neighboring frequency ranges (Fig. 7, 8); 3) higher stability of functional state over time in the *norm* group; 4) higher interindividual consistency of *pathology* group (Fig. 6); 5) difference of pairs of derivations with high synchrony in the two groups of subjects (Fig. 8); 6) higher synchrony in the *norm* group (Fig. 7); 7) a consistent decrease in synchrony from the frontal interhemispheric connections to the occipital ones in both groups (Fig. 7); 8) a difference in topography of hemispheric dominance with its wider spatial representation in *pathology* group (Fig. 8); 9) a strong factor structure of PS in both groups with the predominance of four main factors; 10) a qualitative and quantitative difference in the factors acting in two groups (Fig. 5).

Further, the MEC results were compared with five other well-known synchrony estimates in the literature: coherence [7], inter-segment synchrony [12], correlations between the frequency parts of amplitude and phase spectra [13] and between filtered EEG.

According to the indicators of descriptive statistics, MEC differed favorably from other methods in terms of centering and uniformity of its values distribution in 0–1 region.

The discriminant classification gave the best results in θ, α, β1 domains with 2–3% errors for each group compared to 5.5–28.2% errors when using other methods [14–17]. Statistical modeling showed that the resulting small percentage of MEC errors differs significantly from the random one at the significance level $p<0.005$. Then, EEG measurements of amplitudes in derivations were added to the PS matrices, which led to 100% reliable, error-free classification.

To substantiate the practical significance of the results obtained, a control check was carried out. To do this, the pathology group was randomly divided into two ones in a ratio of 3:2 – the *learning* and *classified* samples. The discriminating function was calculated from *learning* sample, which was then used to assign to a particular group of *classified* subjects. Using of α domain and consistent subgroups of subjects gave the best result: 1.5% of errors in *learning* classification and 6.2% of errors in *control* classification. It should be noted that such important control checks have never been carried out anywhere and by anyone.

b) Schizophrenia [9]

The material included three groups of 8–15 years adolescents: 36 schoolboys without mental disorders (the *norm* N group), the group of 45 patients with the diagnosis of F20 *schizophrenia,* and the group of 80 patients with the diagnosis of F21 *schizotypal disorder*.

The results of the performed complex analysis reveal the complicated picture of regional, interhemispheric differences in EEG synchrony between two schizophrenic disorders and the norm. In particular, most of the patterns listed at the beginning of Section VIIa were confirmed.

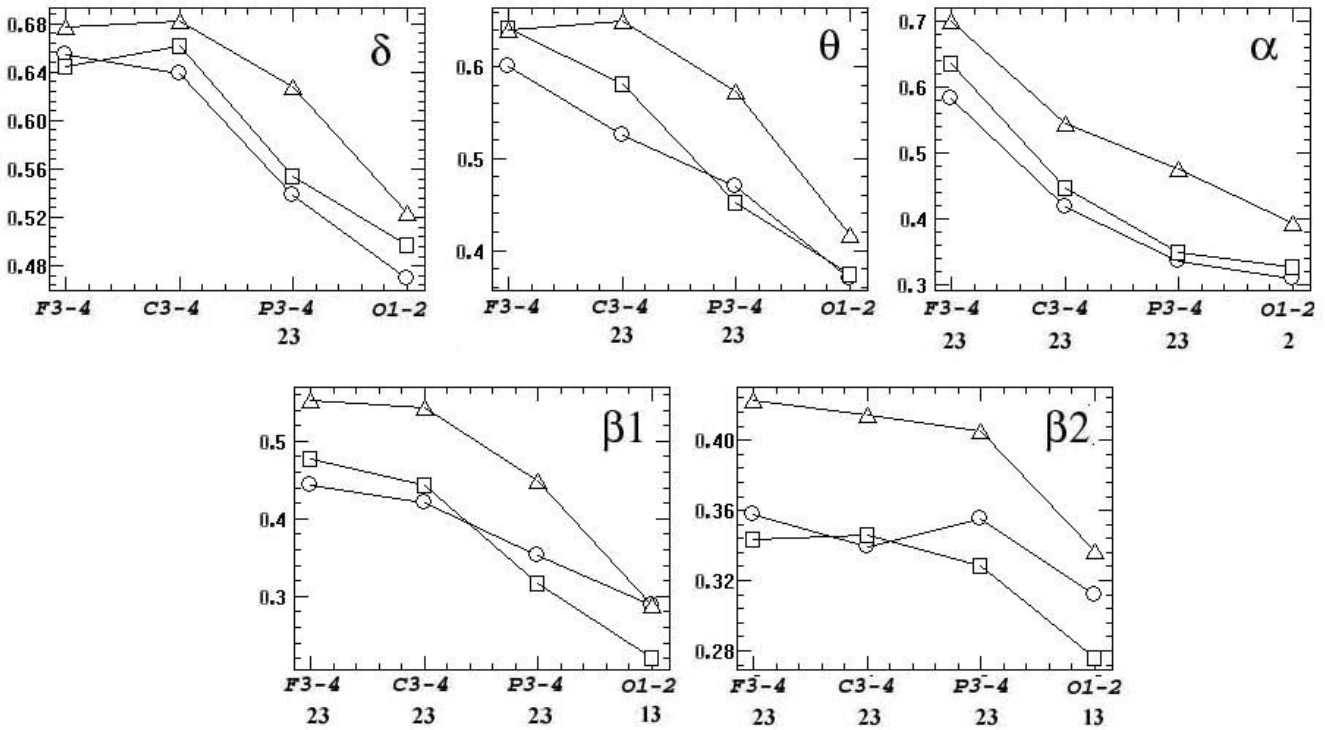

Fig. 7: Differences in interhemispheric synchrony for five frequency domains ($p=0.04—0.0004$). The values averaged for each group, synchrony (vertical axes) are shown for derivation pairs: *F3–F4, C3–C4, P3–P4, O1–O2* (horizontal axes). Group markers: circles – F20, squares – F21, triangles – N. Below graphics, the designation of reliable intergroup differences is shown in number notation: 1 – F20–F21, 2 – F20–N, 3 – F21–N.

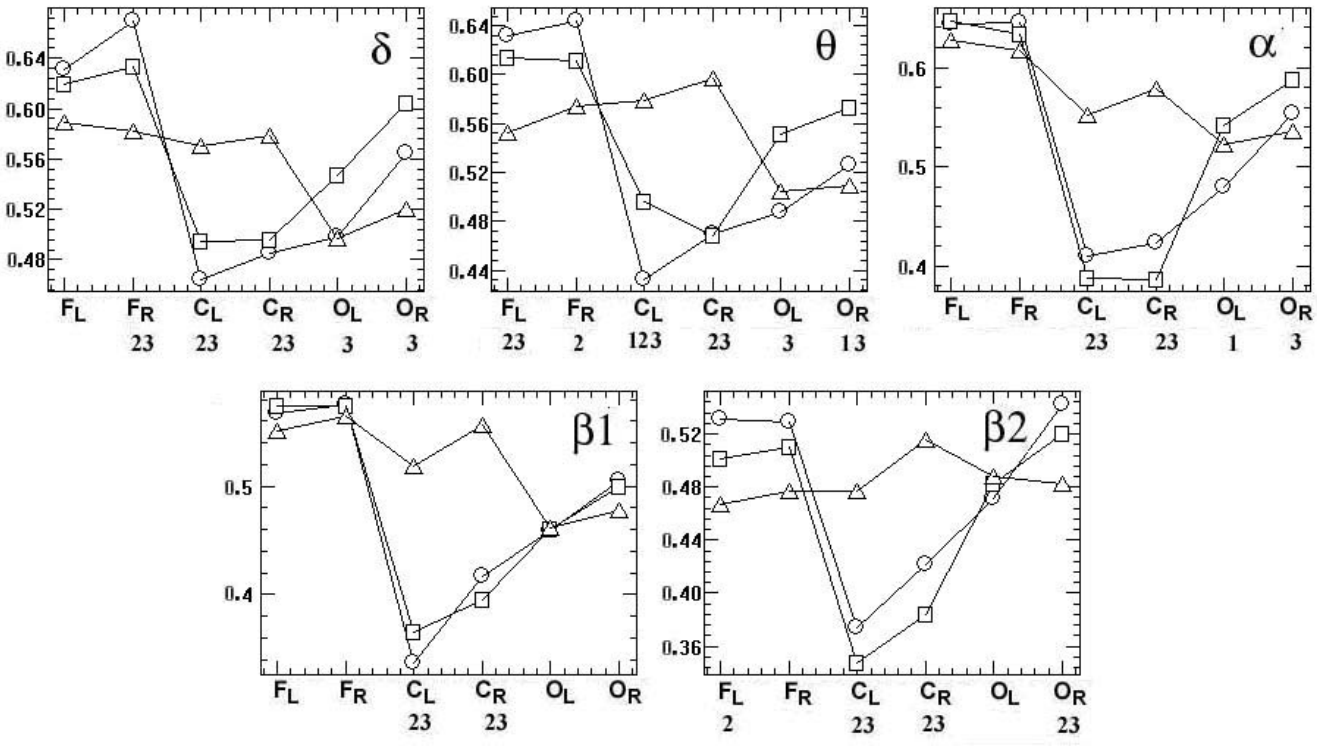

Fig. 8: Regional intrahemispheric differences in frequency domains (p=0.033—10^{-8}). The averaged values of synchrony for each group (vertical) in order of regions (horizontal): F_L, F_R (frontal left and right), C_L, C_R (central left and right), O_L, O_R (occipital left, right) [4], other notations are similar to Fig. 7.

It is necessary to emphasize, that in this study not only the usual problem of differentiation of norm and pathology was considered, but at the same time also the non-depicted earlier in literature more complex task of detection of subtle differences between the two close nosologies. The significant differences between F20 and F21 groups appear mainly in frontal and occipital areas in certain frequency domains. Besides, in occiput, interhemispheric and intrahemispheric synchrony for schizophrenia (F20) in some cases was closer to normal. In contrast, for schizotypal disorder (F21), intrahemispheric synchrony is higher than normal, but interhemispheric synchrony is below than normal. Certain relationships of this kind are also observed in parietal, temporal, and central areas.

One the distinctive and stable component of mental disorders in comparison with the norm is the presence of the vast areas of low synchrony separating isolated frontal and occipital intrahemispheric areas with synchrony near to normal level (Fig. 8). The presence of such a reduction and detection of right-sided asymmetry can indicate a substantial violations of interhemispheric and frontal-occipital relationships for the schizophrenic and schizotypal disorder, which fits into the framework of the well-known theory of disintegration of cortical electrical activity.

The intergroup comparison reveals the crosswise area of the sharp decrease in synchrony of pathology groups ("downfall") in comparison with the norm, including sagittal-interhemispheric and axial-central segments (Fig. 8). It's possible that this indicates significant violations of interhemispheric and frontal-occipital relationships at disorders of the schizophrenic spectrum. When comparing of two pathology groups (F20–F21), in many frequency domains we also observe distinctive regional and interhemispheric areas of increase-decrease of synchrony.

Four psychometric tests were performed on all patients: volume of direct reproduction defined by the technique of memorization of 10 words under verbal presentation; volumes of simple and difficult paired associates; runtime of Schulte tables execution. Indeed, violation of cognitive functions is one of the main consequences of schizophrenia. Several high correlations between psychometric indicators and local estimates of synchrony for each of F20 and F21 groups were revealed.

The main results of discriminant classification are the following: 1) θ domain provides the lowest percentage of classification errors; 2) β2 domain is the next one by its discriminant sensitivity; 3) association of PS of these two frequency domains gives the exact

[4] e.g., F_L region comprising the synchrony values between *F7, F3, T3, C3* derivations; C_L, region including synchrony between *T3, C3, T5, P3*; O_L region including synchrony between *T5, P3, O1*, etc.

classification of three groups without any errors. The obtained results favorably differ from sevaral of alternative approaches using other indicators and more sophisticated methods – see in Section VIIa. It should also be emphasized, that the efficiency for classification of θ domain was also found in the previous study.

Numerous confirmations of the results of the previous study in different groups of patients indicate the stability and effectiveness of MEC compared to the above-mentioned randomness of the coherent analysis results.

c) Depression [10]

The material included two groups of older adults aged 49–82 years: 1) 11 men and 40 women with the psychogenically provoked depressive reaction of bereavement: category F43.21 according to ICD-10, HDRS=22±5.09 on Hamilton scale; 2) a control group of 18 men and 11 women without depressive disorders.

The results of the analysis revealed a complex picture of regional and interhemispheric differences in EEG synchrony between the norm and depressive deviations, including different ratios of greater—less or the same synchrony in activity of different cortical zones. One of the principal features of the obtained integral picture is the presence of extended zones of sharply reduced synchrony of neurophysiological activation processes in depression, covering the entire premedial region in the forehead–occipital direction, including interhemispheric connections, as well as lateral frontotemporal connections in both hemispheres. In the same time, a single topographic picture of changes in EEG synchrony during depression is reproduced in general terms in all frequency domains. This indicates a deep deprivation in depressions of frontal-occipital, frontal-temporal and interhemispheric interactions throughout in sagittal direction.

There is a general decrease in sagittal directions with signs of left-sided asymmetry. This indicates that greater activation of right hemisphere, which causes the predominance of negative emotions in depression, maybe enhanced with a greater discoordination of processes in the right hemisphere.

In addition, an increase in synchrony was revealed in several of axially directed intrahemispheric pairs of derivations primarily in temporo-central and temporo-parietal ones. This may indicate an increase in systemic coordination between auditory and somatosensory sensitivity in the primary projection areas and in the associative posterior temporal and parietal zones. On the other hand, a decrease in synchrony in sagittal anterior-posterior-temporal and central-parietal pairs of derivations may indicate a deprivation of systemic coordination between the processes in the areas of primary projection of the auditory and tactile analyzers and the associative processes of integrated perception of corresponding sensations. About the primary and associative visual areas, such synchronization-desynchronization phenomena are not observed.

It should be particularly noted that a similar picture of differences in norm and pathology was also revealed in the study of schizophrenia, where there was also an extended interhemispheric and premedial-sagittal zone of decreased synchrony from the forehead to the back of the head with a compensatory increase in correlation synchrony in axially conjugated pairs of derivations. This indicates the similarity of changes in synchrony of neurophysiological activation processes in these two types of mental disorders.

This similarity of changes looks even more convincing considering that the topography of correlation synchrony distribution in the group of healthy adolescents had significant differences from the group of healthy older adults. This suggests that MEC detects similar changes in different forms of pathology and in different age groups. This stability compares favorably with the heterogeneity of the results obtained when using coherence function in studies of depression and schizophrenia.

In discriminant classification, the use of δ, θ, β 2 frequency domains allows to accurately separate the records of two studied groups without any errors. Recall that θ, $\beta 2$ domains were also the best ones for classification of schizophrenia, which once again confirms the stability of MEC results The only alternative classification of norm and depression using estimates of spectral power and coherence [18] was accompanied by 8.7% of errors.

d) Sleep stages [11]

The material included many hours of sleep recordings for 15 right-handed men aged 18–34. Seventy-five 20-second fragments were visually selected for each of 5 sleep stages W, 1, 2, 3/4, REM according to Rechtshafen—Kale criteria. The five PS matrices calculated from these fragments were the source material for subsequent cross-analysis.

In addition to numerous particular regularities, the following significant results were obtained: 1) left-hemisphere dominance in all stages of sleep, which is natural for right-handed subjects and indicates the effectiveness of MEC; 2) the dominance of the frontal regions over the occipital ones; 3) differences in the synchrony ratios for sleep stages in different frequency domains; 4) differences in the patterns of synchrony changes in interhemispheric connections from the forehead to the occipital ones; 5) topographic features of localization of highly synchronous connections by sleep stages and frequency domains; 6) significant topographic difference of W stage from other stages; 7) close topography is observed: in θ domain for all stages; as well as in stages 2 and 3/4 for all frequency domains.

Discriminant classification with expanded data matrices, when amplitude indicators were added to PS matrices, revealed an average of 11% errors, and classification errors of individual stages were in the range of 3–20%. This is significantly better than the results of four similar publications using other methods, where the classification errors of various stages were 5–42% [19–22].

Additionally, a control check was performed when the records of each sleep stage were divided into two groups in the ratio of 80 to 20% – a learning and a classified sample. The number of classification errors of the learning sample was 7%, and the attribution errors of the classified sample were 18.3%. This seems to be a completely acceptable result, which is absent in other publications.

VIII. Conclusion

The results presented in Sections VIIa–VIId exhaustively and comprehensively substantiate the thesis formulated in the title of the article.

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We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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