# A Qualitative Study to Explore the Role of Olfactory Stimulant Plants in Modulating IL-6 in Post-Traumatic Stress Disorder (PTSD) and Traumatic Brain Injury (TBI)

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**Background:** Numerous research studies have confirmed that there are physical and mental benefits associated with performing therapeutic horticulture (TH) activities [1] . Studies have proven that therapeutic horticulture interventions successfully improved psychological wellbeing of patients living with PTSD, TBI, substance abuse, and depression [2]. However, there are no clear studies to show how the special characteristics of certain therapeutic plants initiate the changes in macrophages to modulate elevated IL-6 levels that are associated with PTSD and TBI in patients. The purpose of this study is to investigate the role of olfactory stimulant plants on macrophages in modulating IL-6 in PTSD and TBI induced neuroinflammation.
**Method:** At a local hospital in Charlotte, North Carolina, we built smell scape gardens and invited 15 patients between the ages of 50 to 85 to spend time with the olfactory and visual stimulant plants. The self-reported survey evaluated the effect of the physiological recovery effects of olfactory, visual, and tactile simulation associated with therapeutic plants on the psychological wellbeing of patients living with posttraumatic stress disorder, substance, alcohol abuse, and depression.
**Results:** The survey results supported the proposal that therapeutic horticulture (TH) is effective in increasing mental well-being, engagement, and a sense of meaningfulness and accomplishment of participants. All the participants in the focus group reported a reduction in stress and anxiety.
**Conclusion:** Although this study's approach to gather qualitative feedback through interviews, limited focus group surveys and conversations was certainly a step in the right direction, no quantitative data gathering was undertaken driven by limitations in accessibility to patient data. To truly validate the impact of olfactory stimulating gardens on macrophages to modulate the elevated IL-6 levels in PTSD and TBI induced neuroinflammation, thorough quantitative research coupled with large scale studies must be conducted.

## Introduction

### Background & Context

Posttraumatic stress disorder (PTSD) and Traumatic Brain Injury (TBI) are devastating diagnoses which affect millions globally [3],[4]. Nearly 69 million people are diagnosed with TBI around the world [5]. Interestingly, TBI and PTSD demonstrate high levels of comorbidity [6]. TBI and PTSD both show notable neuroinflammation and subsequent excitotoxicity, oxidative stress, and morphological changes [7]. Studies have been conducted to prove the role of elevated IL-6 in neuroinflammation [8],[9]. This study focuses on the factors promoting neuroinflammation in PTSD. Given the role of IL-6 in neuroprotection acutely, compared to detrimental chronically, targeting this cytokine at specific time points may be beneficial in modulating neuroinflammation [7]. Present treatments for TBI or PTSD are variably effective [10]. Given the role of IL-6 in PTSD, ongoing research is required to establish non pharmaceutical treatments to modulate IL-6 in patients with PTSD, TBI, and other neurological disorders. This research study focuses on the impact of TH intervention in overall psychological well-being in the participating patients.

TBI is defined as a brain injury due to external force [11], whereas PTSD is more related to emotional trauma involving intrusive thoughts, avoidant behavior, guilt, and apathy [12]. Due to the etiology of these diagnoses, however, they frequently occur together. Intriguingly, isolated PTSD and post-TBI patients have similar clinical presentations, with both showing anxiety, irritability, insomnia, and cognitive deficits [6]. This symptom overlap may be attributable to similar pathophysiology [7].

### Neuroinflammation in TBI and PTSD

TBI has been shown to increase levels of M1 microglia, which are pro-inflammatory derivations of myeloid precursor cells [13],[14] These microglia release inflammatory cytokines, including IL-1, IL-6, IL-12, TNF-$\alpha$, and IFN-$\gamma$, which ultimately perpetuate a cyclic proliferation of M1 microglia [15],[16]. While acute neuroinflammation can induce neurogenesis, increase spatial learning,

and decrease infection risk, it can become detrimental if prolonged[17,18]TBI presents with acute and chronic neuroinflammation[19].

Similarly, pro-inflammatory microglia promote neuroinflammation in PTSD[20]. PTSD-related microglial proliferation, however, can be seen after stressful events, with chronic stressors further amplifying the differentiation of pro-inflammatory microglia[21]. PTSD also shows BBB damage, like TBI4. TBI and PTSD share many consequences of prolonged neuroinflammation, such as altered synaptic transmission, changes in morphology, and changes to neuronal plasticity[22,23]

## Role of IL-6 in Neuroinflammation

The role of IL-6 in neuroinflammation is variable. However, two cell signaling pathways help to explain the dual-acting impact of IL-6[24].

In classical signaling, IL-6 binds to the membrane-bound IL-6 receptor (IL-6R) on the surface of target cells. This complex then associates with the signal-transducing receptor subunit gp130, initiating downstream signaling pathways[25,26]Classical signaling is generally associated with regenerative and protective responses. It plays a crucial role in immune regulation, hematopoiesis, and tissue regeneration[27,28]

In trans-signaling, IL-6, as a modulator of inflammation[24], binds to a soluble form of the IL-6 receptor (sIL-6R). This IL-6/sIL-6R complex can then interact with gp130 on the surface of cells that do not express IL-6R, thereby initiating signaling in a broader range of cells[29].

Neuroinflammatory cells have gp130 but not membrane bound IL-6 receptors and thus require this soluble receptor/IL-6 complex to promote inflammation[24]. This differential signaling mechanisms offer niche therapeutic possibilities to reduce neuroinflammation. For TBI and PTSD, elevated IL-6 may offer novel treatment options given these findings on IL-6 signaling[30].

## IL-6 in patients with PTSD

Given the similar neuroinflammatory phenotypes between TBI and PTSD, it is not surprising that IL-6 is also reportedly elevated in PTSD[31]. In patients with PTSD compared to patients without, there were higher salivary pro-inflammatory cytokines, IL-2, IFN-$\gamma$, IL-6, and IL-17, and lower anti-inflammatory cytokines, IL-4 and IL-10[32]. This continuous hyperactivation may promote chronic inflammation detrimental to patients with PTSD. Health quality of life measurements was also notably decreased for patients with higher levels of IL-6 and PTSD[33]. Not only do elevations in IL-6 impact the pro-inflammatory cascade seen in PTSD, but it may also cause a plethora of devastating PTSD symptoms. Overall, IL-6 is clearly elevated in PTSD, likely contributing to symptoms and severity.

## Treatments Targeting IL-6 for PTSD and TBI

Current treatments for PTSD and TBI are moderately, but inconsistently and incompletely successful. TBI treatment includes rest or surgery (in severe cases)[10]. While these treatments may be beneficial, they may not rectify the permanent neurological damage resulting from neuroinflammation[30]. PTSD treatments are broader, including psychological approaches, such as narrative exposure psychotherapy and pharmaceutical approaches, such as SSRIs[34,35]

Underlying neuroinflammation in PTSD and TBI may explain the similarity in symptoms. Furthermore, a common therapeutic target may be capable of mitigating TBI and PTSD symptoms. A therapy to target both PTSD and TBI would be incredibly beneficial due to the comorbidity of these disorders[7]. A potential target for the neuroinflammatory cascade is IL-6, a cytokine involved in inflammation[36,37]. Unfortunately, about half of the patients do not benefit from current treatment modalities. Given $IL-6's$ apparent role in the pathology of PTSD and TBI, it is a promising target for non- pharmaceutical methods.

## Role of Olfactory Receptors & Macrophages in resolution of inflammation

Olfactory receptors (ORs) were initially described in 1991 by Linda Buck and Richard Axel. In their initial observation, they suggested that this new family of receptors was restricted to the olfactory epithelium (OE) of the nose[38]. These G-protein-coupled receptors (GPCRs) are activated by volatile chemical compounds also known as odorants[39]. ORs in humans are proposed to be able to discriminate between anywhere from 10,000 to more than one trillion different smells[40]. Intriguingly, ORs were found expressed also in macrophages in both mice and humans[41,42]

The olfactory system (in the brain) is closely connected to the limbic system, involving neural regions like the hippocampus, amygdala, and thalamus. Consequently, olfactory perception is also closely tied to emotional and stress processing and smell-related autobiographical memories; associated emotional encodings are also retrieved with stronger activation of the amygdala beyond non-emotional memories or emotional memories associated with other modalities. Consistently, perceived smells that are not actively attended to are also able to evoke emotional responses in individuals[43].

Monocytes and macrophages have a highly specialized sensory system of pattern-recognition receptors, GPCRs, and tyrosine kinase receptors[44]. Among the GPCRs, ORs can "smell" metabolites and allow macrophages to respond to their environment. This response can, among others, mediate the activation of the inflammasome[41]that is also highly conserved among vertebrates[45]

Macrophage origin can be broadly divided into tissue-resident macrophages and monocyte-derived macrophages[41].

Macrophages can have proinflammatory or anti-inflammatory features, defined often as classical M1 (proinflammatory) or alternative M2 (anti-inflammatory) polarization. During inflammation and damage, derived monocytes can populate the inflamed tissue, generating dendritic cells (DCs) and macrophages that impact the initiation, progression, and resolution of inflammation[41].

### Objective

**Non-pharmaceutical treatments targeting IL-6 in patients suffering from PTSD**

Therapeutic Horticulture (TH) has been applied as one of most common non-pharmaceutical intervention to enhance the health of elder people. TH is contacting with nature and associated physical activities such as growing and eating food together and TH has long been several ways to increase mood, improve nutritional status, reduce loneliness, and reduce the physical health impacts of mental illnesses such as post-traumatic stress disorder[46]

Extensive studies have proven that TH is associated with a reduction in the levels of biomarkers that measure the extent of T-cell exhaustion and inflammation in older adults. The positive effects of TH on T-cell exhaustion were associated with the reduction of IL-6 levels[46].

Researchers have found that plant scents stimulate nerves in the brain through the olfactory sulci, inducing the central nervous system and endocrine system to secrete hormones, thereby affecting various physiological reactions[43].

As shown in Table 1, all three types of stimulation affected the central nervous system, which can be seen from the ANOVA results for the $\alpha$ and $\beta$ brainwave amplitudes. The ANOVA results suggest that during exposure to the olfactory, visual and olfactory–visual stimulus modes, the subjects' alpha and beta brainwave amplitudes exhibited significant increases compared with the control group. Olfactory receptors in macrophages are a rich source of untapped opportunity for modulating inflammation and reducing elevated Il-6 levels associated with PTSD and other neurological disorders[41]. I hypothesize that special characteristics of certain therapeutic plants could initiate the changes in macrophages to modulate elevated IL-6 levels, and the modulated IL6 levels could potentially improve the wellbeing of patients with neurological problems such as PTSD and TBI.

## Methodology

Therapeutic horticulture (TH) has only been recently introduced at the hospital which I conducted the study at. Under the guidance of a horticultural therapist, sensory gardens have been created with an intent to stimulate senses and create a multisensory healing experience at this hospital. A sensory garden is a garden that stimulates the senses of sight, smell, sound, taste, and touch. The goal of a sensory garden is to encourage visitors to interact with the garden and experience it with all their senses. Given the limited time and restricted access to patient data, self-reported survey was identified as the most appropriate methodology to test the hypothesis that olfactory stimulating plants on macrophages potentially play a significant role in modulating IL-6 in PTSD and TBI induced neuroinflammation. The emphasis of this research was more on personal narrative, interviews, patient feedback, and Horticultural Therapist's observations.

### Preparation and Material

The sensory garden at the hospital was made possible because of the efforts of several volunteers, including staff, volunteers like myself, and patients – all contributing time, materials, equipment, and services needed to create the garden – a process which occurred over a 12-month period. Through this process of building the sensory garden, the horticultural therapist sought ideas and inspiration as well as practical advice on plant selection from both academic and popular literature. In addition, the horticultural therapist regularly talked with patients about the purpose of the garden to generate interest and involvement.

A couple of locations were identified for the creation of the garden primarily to meet two objectives. First, the garden should provide a positive retreat for patients and visitors. Second, a dedicated space was required where plant selection and therapeutic horticulture (TH) activities can be discussed with the participants. With these two criteria in mind, the open space next to and existing Green House in the hospital was narrowed down as the final location for the sensory garden.

Also, several key features were considered as part of the garden design, including plant selection and equipment selection to be appropriate for the patients suffering with PTSD, TBI, Substance Abuse, and/or depression (see Table 2).

### Participants

In this study, 15 patients between the ages of 50 to 85 were interviewed at the hospital. The patients have been informed of the purpose of this study and have willingly contributed to report on the findings through focus group surveys and interviews. Further, the patients have been assured that confidentiality will be maintained on their personal information and medical conditions. The15 participating patients are geriatric, suffering from PTSD, depression, and alcohol/substance abuse. This assessment was taken after the participants visited the newly designed therapeutic sensory garden for at least once a week consistently over a period of 6 months.

**Table 1** Significance analysis of the influence of different stimulation methods on skin conductance (SC), $\alpha$ waves and $\beta$ waves

| | | P (LSD) | | |
|---|---|---|---|---|
| | | **O** | **V** | **O&V** |
| **SC** | O&V | 0.004 | - | - |
| | C | - | 0.001 | 0 |
| **$\alpha$ waves** | O | - | 0.006 | - |
| | C | 0.009 | 0 | 0.001 |
| **$\beta$ waves** | V | 0.001 | - | 0.006 |
| | C | 0.01 | 0 | 0.001 |

$p < 0.01$ indicates an extremely significant difference; $0.01 < p < 0.05$ indicates a significant difference; $p > 0.05$ indicates that the difference was not significant. Those not shown were a combination of $p > 0.05$. O: olfactory stimulation; V: visual stimulation; O&V: olfactory–visual stimulation; C: control; SC: skin conductance.

### Intervention

The therapeutic horticulture (TH) intervention was designed by the horticultural therapist at the medical center. Patients were directly involved in planting and maintaining the sensory garden. Tasks included planting and raising flowers, herbs, and vegetables from seeding, watering, mulching and weeding. Other horticultural activities such as pruning the Bonsai trees, watering the hanging baskets, and setting up climbing plants by trellis were also included to gauge and enhance patients' engagement and interest. The patients were then encouraged to spend time at the Substance Abuse Recovery and Rehabilitation Treatment Program (SARRTP) garden to test the impact of olfactory stimulant plants such as White Gaura (Oenothera lindheimeri), Bee balm, and Lavender plants. Tactile stimulant Lamb ears plants were also planted in the garden to allow veterans to touch and feel those plants during the visits to the garden. It is to be noted that the horticultural therapist worked very closely with the participants to explain the various uses of plant species in the sensory gardens. Therefore, patients were fully aware of the smell sources, tactical stimulants and were voluntarily spending time at the garden and participating in the horticulture activities during the process of building the garden and through the study period of 6 months.

### Patient interviews, conversations and reflections

As previously mentioned, due to constraints on availability of patient data combined with the exploratory nature of this project, qualitative data collection methods such as patient interviews, surveys, and reflections were used to evaluate the impact of sensory gardens as opposed to quantitative analysis. The participants who were involved in the sensory garden implementation and the participants who took part in the weekly sessions were asked to fill in surveys to provide information on why they came to these sessions, what they enjoyed most about the newly created garden(s), how they used this space, and the impact of the TH program on specifically their mental well-being. The horticultural therapist at the hospital also conducted in-depth conversations with the participants during the 6 months program to understand the impact of sensory gardens on stress and anxiety, engagement and participation, mental well-being and social exchange.

### Study Results

The study results directly supported the hypothesis that spending time at the newly created sensory garden certainly had positive effects such as increasing mental well-being, engagement, and a sense of meaningfulness and accomplishment as reported by the participants. Many participants reported a reduction in stress and anxiety that allowed them to slow down and enjoy nature, trigger a memory, feel more positive and experience a sense of more balanced state. Intriguingly, the patients who do not like gardens are also the same people who sit indoors and do not seek out a social support. They are reluctant to make a change in their environment and are also the more likely to have repeat admission for the same issues such as drug rehabilitation treatment and other mental disorders.

When reviewing the feedback provided by the 15 participants over the 6-month period, several themes were identified across the interviews, surveys and personal reflections. Table 3 summarizes the survey results by the plant and stimulation type.

**One major theme is that the sensory garden provided an opportunity for some patients to feel more capable:**

*"I feel a sense of accomplishment from making art with my bonsai plant"* (Patient with Depression).

**Secondly, the horticultural activities provided an opportunity for new experiences and skills:**

*"I have never gardened before, and I am finding that horticulture is fun"* (Geriatric Patient).

**Third, the smell scape garden(s) triggered old memories and had the patients longing for more:**

**Table 2** Key considerations in designing the sensory garden

| |
|---|
| **Garden Design:** The garden should be an attractive and interesting location for spatial engagement with below key considerations:<br>• Garden should encourage physical and passive engagement with the space.<br>• Most spaces should be accessible to patients of all abilities.<br>• Layer in some potential seating areas (in shady spots) for comfort and to encourage interactions.<br>• Different zones for one-to-one and group use by patients, families, and therapist-patient sessions.<br>• Raised garden beds at accessible heights for seated gardening. Raising the soil level three feet is a good height for both adult wheelchair users and standing veteran gardeners<br>• Levelled pathways (with minimal slope) for easy cane, walker or wheel chair maneuvering. |
| **Equipment Selection:** Below are some equipment and accessories consideration to enable a therapeutic gardening experience for the veterans:<br>• Correct table heights for manual and power wheelchair access.<br>• Appropriate height for chairs and benches to enable patient transfer to and from wheelchairs.<br>• Light weight, brightly colored tools and watering cans that are interchangeable, and adjustable to be used by veterans with a wide range of abilities.<br>• Hose spigots should 2-3 feet above the ground for ease of access by individuals using a wheelchair<br>• Retractable hose that covers entire area.<br>• Lever faucet handles are preferred over knob handles as they are easier to turn on and off. |
| **Plant Selection:** Overall, the plant palette should help patients narrate interesting stories about their life experiences, bring back beautiful memories, and make sense of current life experiences through optimal olfactory stimulation.<br>• Touching plants with unique and soft textures such as Lamb's ear and Silver sage (Salvia argentea 'Artemis').<br>• Culinary plants (i.e. Tomatoes, bell peppers, mint, sage, lavender, thyme, zucchini) that provide patients with opportunities to be a part of the entire lifespan of these plants – from sowing seed to growing them in the garden, and then harvesting and eating - triggering a sense of accomplishment.<br>• Incorporate plants with bright colors like petunias, sunflowers, and cosmos to energize patients, while blue or white colored flowers like salvia, bluebells, hyacinth, jasmine, and chamomile can de-stress.<br>• Ornamental grasses (White Pampas, Pink Muhly, Bunny tail grass) gracefully respond to the breeze and help patients immerse in the gentle sound and texture of these delicate grasses.<br>• Plants for tranquility and relaxation such as Bonsai, Pothos, Jade, Wandering Dude, and Succulents.<br>• Flowering perennials (Roses, zinnias, lilies, hydrangeas, daisies, ornamental gaura) that not only are a visual treat but also attract bees, humming birds, and butterflies to flock to their nectar-rich blooms. |

*"My mom has always gardened when I was younger; I feel like this is a great way to honor her memory"* (Patient with PTSD).

**Fourth, multiple participants reported feeling more hopeful and increased patience levels:**

*A participant with PTSD was particularly impressed with how simple yet so deeply satisfying it was to grow tomatoes right from the seeding stage and then patiently wait for them to be harvested.*

**And finally, the sensory garden activated the senses by providing exposure to fresh air, familiar touch, new smells and sunlight:**

*"I enjoy the outdoors, and I enjoy gardening and the smell of lavender reminds me of my childhood."* (Alcohol abuse patient).

*"The gently touch of the Lamb's ear reminds me of my daughter when she was a baby"* (Geriatrics Patient).

## Conclusion

As evidenced by the study results, therapeutic horticultural sensory garden has proven to make a significant positive contribution at the hospital. This review highlights that non-pharmaceutical interventions like therapeutic horticulture (TH) within an acute healthcare setting can improve the health out-

**Table 3** Summary of survey results by the plant and simulation type

| Plant | Stimulation | Impact | Patient Condition | Frequency of visit | Observations |
|---|---|---|---|---|---|
| **Gaura** | Attracts butterflies and sways in the wind | Attracts animals, such as butterflies, which the veterans enjoy watching | PTSD | 1/week | Allowed them to slow down and enjoy nature |
| **Bonsai (Jade)** | Calming, meditative | Teaches patience, perseverance, and determination | Alcohol abuse, depression | Every day | Patients keep them in their rooms and watch them grow every. Sense of accomplishment from making art with plants |
| **Bea Balm** | Olfactory Stimulation | Activates sense of smell and allows the veterans to enjoy nature, such as bees visiting the plant | TBI, Substance abuse | 1/week | Allowed them to slow down and enjoy nature, trigger a memory and think what other plants may smell like this |
| **Tomatoes** | Memory Stimulation | Most people have found memories gardening with family | TBI, Depression | 1/week | See fruits of their labor, reminiscence about good times growing up with a garden |
| **Lavender** | Olfactory Stimulation | Activates sense of smell: known for its ability to help relaxation | PTSD | 1/week | Allowed them to slow down and enjoy nature, trigger a memory what other plants may smell like this |
| **Lamb's Ear** | Tactile Stimulation | Activate sense of Touch | Geriatrics, Depression | 1/week | Allowed them to slow down and enjoy nature, trigger a memory what other plants or material they resemble in their lives, or something interesting |
| **Succulents (Various species)** | Hardiness | Relatedness | PTSD, Substance Abuse | Every day | Patients keep them in their rooms and watch them grow every day. Easy to grow, requires little water. Patients can relate to hardiness of plant and the possibility of overcoming an adversity. |
| **Hanging Basket house plants (Pothos, wandering dude)** | Symbolize: hang in there | Relatedness | TBI Depression | Every day | Patients keep them in their rooms and watch them grow every day. Easy to grow, requires little water. Patients can relate to hardiness of plant and the possibility of overcoming an adversity. |

comes for patients with psychiatric disorders. In addition, the findings from this review support the possibility that olfactory stimulation through healing gardens could potentially modulate inflammation and reduce elevated IL-6 levels in patients with neurological disorders such as PTSD and TBI.

However, this review is subject to some limitations. Due to constraints on time and data, only a limited pool of 15 patients were enrolled in this study. More patients should be included in future studies to further evaluate the results. Further, this study revealed positive outcomes for the participant pool based only on short-term TH activities. Future large-scale studies need to measure the long-term effects of sensory gardens on physical and mental health of the vulnerable veteran pool.

Furthermore, although this study's approach to gather qualitative feedback through interviews, limited focus group surveys and conversations was certainly a step in the right direction, no quantitative data gathering was undertaken driven by limitations in accessibility to patient data. To truly validate the impact of olfactory stimulating gardens on macrophages to modulate the elevated IL-6 levels in PTSD and TBI induced neuroinflammation, thorough quantitative research couple with large-scale study must be conducted. It would be valuable to obtain access to participants' neurological data and then analyze the IL6 levels in those participants both pre- and post- exposure to olfactory stimulation. Determining the connection between olfactory receptors, TH sensory gardens and impact on elevated IL6 levels associated with neurological disorders such as TBI and PTSD would be a great milestone in supporting communities.

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## Definitions

**M1 microglia** are a type of activated microglia that are pro-inflammatory and can cause neuronal damage and degeneration. They are one of two main phenotypes of microglia, the other being M2 microglia, which are anti-inflammatory
**Myeloid progenitor** cells are the precursors of red blood cells, platelets, granulocytes (polymorphonuclear leukocytes [PMNs]: neutrophils, eosinophils, and basophils), monocyte-macrophages, dendritic cells (DCs), and mast cells and osteoclasts.
**Neurogenesis** is the process by which new neurons are formed in the brain. Neurogenesis is crucial when an embryo is developing, but also continues in certain brain regions after birth and throughout our lifespan
**Neuroinflammation** is the process by which an organism attempts to remove an injurious stimulus in the central nervous system (CNS) and initiate the healing process to protect the cells and overall function of the brain.
**Signaling pathway** refers to a series of molecular interactions that occur within the nervous system to transmit signals and regulate various processes
**Excitotoxicity** This occurs when there is excessive activation of excitatory neurotransmitters, primarily glutamate. High levels of glutamate lead to prolonged activation of glutamate receptors, such as NMDA receptors, resulting in an excessive influx of calcium ions into neurons. This can cause neuronal damage and cell death. The neuronal damage caused by excitotoxicity can trigger an inflammatory response in the brain. Microglia, the brain's resident immune cells, become activated and release pro-inflammatory cytokines, such as IL-1, TNF-, and IL-62. This inflammation can further exacerbate neuronal damage and contribute to a cycle of ongoing neuroinflammation and excitotoxicity.
**Oxidative Stress** This occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage. ROS are highly reactive molecules that can damage cellular components, including lipids, proteins, and DNA. The damage caused by oxidative stress can activate microglia and astrocytes, the primary immune cells in the brain. These cells respond by releasing pro-inflammatory cytokines such as IL-1$\beta$, TNF-$\alpha$, and IL-6, leading to neuroinflammation.
**Cytokines** are small proteins that play a crucial role in cell signaling, particularly within the immune system. Interleukin-6 (IL-6) is a cytokine, a type of signaling molecule in the immune system, that plays a significant role in the body's inflammatory response.
**Microglial proliferation** plays a significant role in the development and progression of post-traumatic stress disorder (PTSD). Studies have shown that microglia are the major brain immune cells responding to PTSD. Their numbers and the ratio of microglia to other immune cells significantly increase following traumatic events.
**Blood-brain barrier (BBB)** is a crucial protective layer that separates the brain from the bloodstream, maintaining the brain's delicate environment. Damage to the BBB can have significant implications for brain health
**Altered synaptic transmission** refers to changes or disruptions in the normal process of communication between neurons. Changes can occur at different stages of synaptic transmission, including neurotransmitter release, receptor binding, and neurotransmitter reuptake or degradation.
**Neuronal plasticity**, also known as neuroplasticity or brain plasticity, is the brain's remarkable ability to reorganize itself by forming new neural connections throughout life. In PTSD, neuroplasticity can be altered, leading to persistent changes in how these brain regions communicate. This can result in heightened fear responses, difficulty in distinguishing between past and present threats, and impaired emotional regulation
**Glycoprotein 130 (gp130)**, also known as IL6ST, is a crucial transmembrane protein that acts as a signal transducer for the interleukin-6 (IL-6) family of cytokines. gp130 forms part of the receptor complex for several cytokines, including IL-6, IL-11, IL-27. When IL-6 binds to its receptor (IL-6R), the complex associates with gp130, leading to the formation of a hexametric signaling complex
**Biomarker** is a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.
**T-cell** immunosenescence refers to the gradual deterioration of the immune system associated with aging, particularly affecting T cells. Senescent T cells tend to produce more pro-inflammatory cytokines, contributing to a state of chronic low-grade inflammation.
**Macrophages** are specialized cells involved in the detection, phagocytosis and destruction of bacteria and other harmful organisms. In addition, they can also present antigens to T cells and initiate inflammation by releasing molecules (known as cytokines) that activate other cells.
**Monocytes** are a type of white blood cell that play a key role in inflammation and the immune system. Monocytes differentiate into different types of cells depending on the local environment. For example, classical monocytes differentiate into pro-inflammatory macrophages, while non-classical monocytes differentiate into anti-inflammatory macrophages
**Pattern recognition receptors (PRRs)** are proteins that recognize patterns associated with pathogens or damage. They are part of the innate immune system and play a key role in the initial defense against infections.
**G-protein-coupled receptors (GPCRs)** are a large family of cell surface proteins that receive and transduce signals from the outside of the cell into physiological effects. They are the largest protein family in the human genome, making up over 3% of human genes. GPCRs are widely expressed in microglia, the resident immune cells of the central nervous system (CNS). Activation of certain GPCRs can regulate microglial responses to injury or disease, influencing the extent of neuroinflammation
**$\alpha$ waves and $\beta$ waves** In the Central Nervous System (CNS), alpha waves are associated with a relaxed, resting state, typically occurring when eyes are closed and a person is not actively focusing on a task, while beta waves are linked to active thinking, alertness, and concentration, appearing when someone is actively engaged in a mental activity or under stress)
**Tyrosine kinase receptors (TKRs)** play a significant role in neuroinflammation, which is a common feature in various neurological disorders. RTKs such as EGFR and c-Abl are implicated in neurodegenerative diseases. Aberrant activity of these kinases can induce neuronal apoptosis and cell cycle arrest, contributing to neuroinflammation and neurodegeneration3.
**Olfactory receptors (ORs)** are specialized cells in the nose that detect odor molecules and allow us to perceive smell
**The olfactory epithelium (OE)** is a specialized tissue in the nasal cavity that detects odors and sends the information to the brain

 