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Cytokine-Induced Neurogenesis for Bipolar Disorder: A Case Study

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ABSTRACT

Bipolar disorder (BPD), formally called manic depression, is a mental health condition that causes extreme mood swings for which specific brain pathology has not yet been precisely defined. We administered cytokine-induced neurogenesis treatment to a 60-year-old male BPD patient to regenerate GABAergic neurons as well as glutamatergic neurons, which resulted in a successful regeneration of the atrophied hippocampus and disorganized cortical structures of the prefrontal cortex and anterior cingulate cortex, which was associated with improved emotional control and the resolution of electrophysiological abnormalities. To the best of our knowledge, this is the first case report demonstrating that cytokine-induced GABAergic and glutamatergic neurogenesis repairs brain pathology due to BPD and improves emotional control.

Keywords: Bipolar Disorder (BPD), Emotional Control, Cytokine, Neurogenesis, Prefrontal Cortex, Hippocampus, Anterior Cingulate Cortex.

INTRODUCTION

Bipolar disorder (BPD) is a severe affective disorder characterized by recurrent episodes of depression or mania, which significantly impair cognitive function, life skills, and social abilities [1]. The diagnosis of BPD is primarily based on clinical assessment and psychiatric examination, highlighting the urgent need for objective markers to facilitate the diagnosis of BPD [2]. Alterations in cortical functional networks, as identified by resting-state electroencephalography (EEG), have been reported in patients with BPD, in which a greater strength, a greater clustering coefficient (CC), and a shorter path length (PL) in the high-beta band in EEG are detected in BPD patients than in healthy controls [3]. MRI of BPD patients revealed that cortical gray matter was thinner in the frontal, temporal and parietal regions of both brain hemispheres [4], which were correlated with the duration of illness [4]. However, these neurophysiological and morphological abnormalities are not consistently useful for the diagnosis of BPD, so more versatile neurophysiological and morphological criteria are necessary for the accurate diagnosis of BPD.

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Although the causes of BPD are not clearly understood, both genetic and environmental factors are thought to play a role. Genetic factors account for approximately 70–90% of the risk of developing BPD. A genome-wide association study of over 40,000 BPD patients identified 64 associated genomic loci [5]. BPD risk alleles were enriched in genes in synaptic signaling pathways and brain-expressed genes, particularly those with high specificity of expression in neurons of the prefrontal cortex and hippocampus [5]. Environmental risk factors, including a history of childhood abuse, long-term stress, and some types of infections, are also associated with BPD [6].

We have explored the clinical application of cytokine cocktail treatment for neurodegenerative diseases such as Alzheimer's disease [7,8], vascular dementia [9], and frontotemporal dementia [7], but we have not yet reported its clinical application for BPD. This is the first case report showing the clinical application of cytokine cocktail treatment for BPD.

METHODOLOGY

Cytokine cocktail formulation used in this study was designed and developed by Luis Carlos Aguilar Cobos at the Livant Neurorecovery Center, Mexico as described previously [7-11]. In this case study, 3 cytokine formulations were used: Gabatrof (EPI), *Gabatrof (ADPK), and Epatrof (PSY). Cytokines were purified by PHLC from porcine tissues. Porcine hepatocyte growth factor (HGF) and granulocyte colony stimulating factor (GCSF) were enriched in Gabatrof (EPI). *Gabatrof (ADPK) contained HPLC-purified porcine adiponectin in addition to HGF and GCSF. Porcine brain-derived neurotrophic factor (BDNF) was enriched in Epatrof (PSY). The daily dose of cytokine cocktail administered in this case was illustrated in Figure 1. Cytokine cocktail was administered sublingually 3 times per day.

CASE DESCRIPTION

A 60-year-old male, a company president from downtown Tokyo, visited the Ochanomizu Health & Longevity Clinic on August 3, 2018, for the prevention of Alzheimer's disease. On the patient's first visit, the Mini-Mental State Examination (MMSE) indicated normal cognitive function (MMSE 29/30) (Figure 1). Apolipoprotein E (APOE) genotype analysis revealed that the patient was a homozygous carrier of the APOE ε3 allele (genotype ε3/ε3). Cognitive function examination using Cognitrax on August 3, 2018, revealed normal verbal memory, reaction time, motor speed, sustained attention, cognitive flexibility, executive function, reasoning, and working memory (Figure 1).

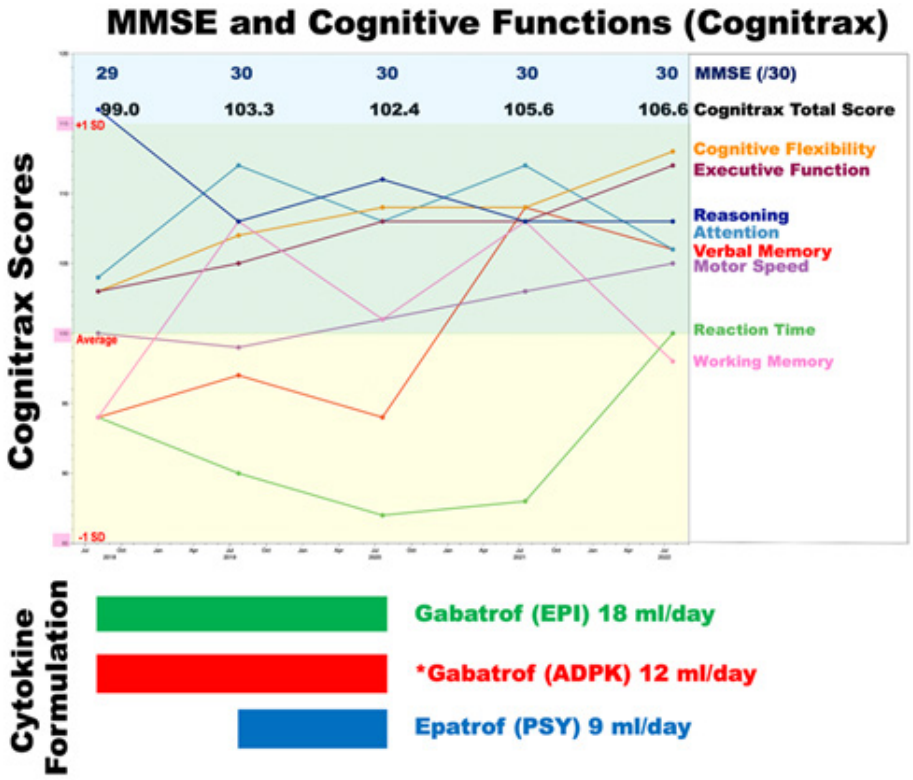

Figure 1. MMSE score and cognitive function before and after cytokine-induced neurogenesis.

Cognitive function was evaluated by CognitraxR and the Mini-Mental State Examination (MMSE) on October 16, 2018; July

23, 2019; July 20, 2020; July 15, 2021; and July 22, 2022. The MMSE scores are annotated in the upper part of the graph. Cognitrax scores for cognitive flexibility (yellow), executive function (brown), reasoning (dark blue), attention (light blue), verbal memory (red), motor speed (plum), reaction time (green), and working memory (magenta) are chronologically illustrated as line graphs with different colors. A Cognitrax score of 100 is the average score among the Japanese population of the same age. Green indicates the zone of the average ± 1 SD, yellow indicates the zone from 1 SD to 2 SD less than the average, and blue indicates the zone + 1 SD over the average. The dose and administered cytokine formulations are shown under the graph.

EEG examination on October 27, 2020, detected slow waves at the frontal, central, and parietal leads at rest (data not shown). P300 EEG data analyzed by Neuroscan Software (https://compumedicsneuroscan.com/) showed that hyperexcitable asymmetric P300 responses were detected at the left frontopolar lead, the left frontolateral lead, the right central lead, the left central lead, the left temporal posterior lead, the left parietal lead, and the left occipital lead after a target stimulus of high-pitched sound (Figure 2A, red line, indicated by red arrows). The magnification of the recordings from the left frontopolar lead in Figure 2A shows a hyperexcitable P300 response with a peak voltage of 400 μV^2 at 200 msec (Figure 2A, red line). The attention test showed a hyperreactive reaction in the left frontopolar lead with a peak voltage of 1,000 μV^2 compared to the control reaction with a peak voltage of 300 μV^2 (Figure 2C, red lines and blue line). As shown in Figure 2D, emotional control analysis revealed that the patient was hyperreactive to all evaluated emotions, including joy, sadness, happiness, neutral feelings, and anxiety, while sad feelings exceeded other feelings, including joy, suggesting that the patient's mood had swung to depression (Figure 2D, left panel).

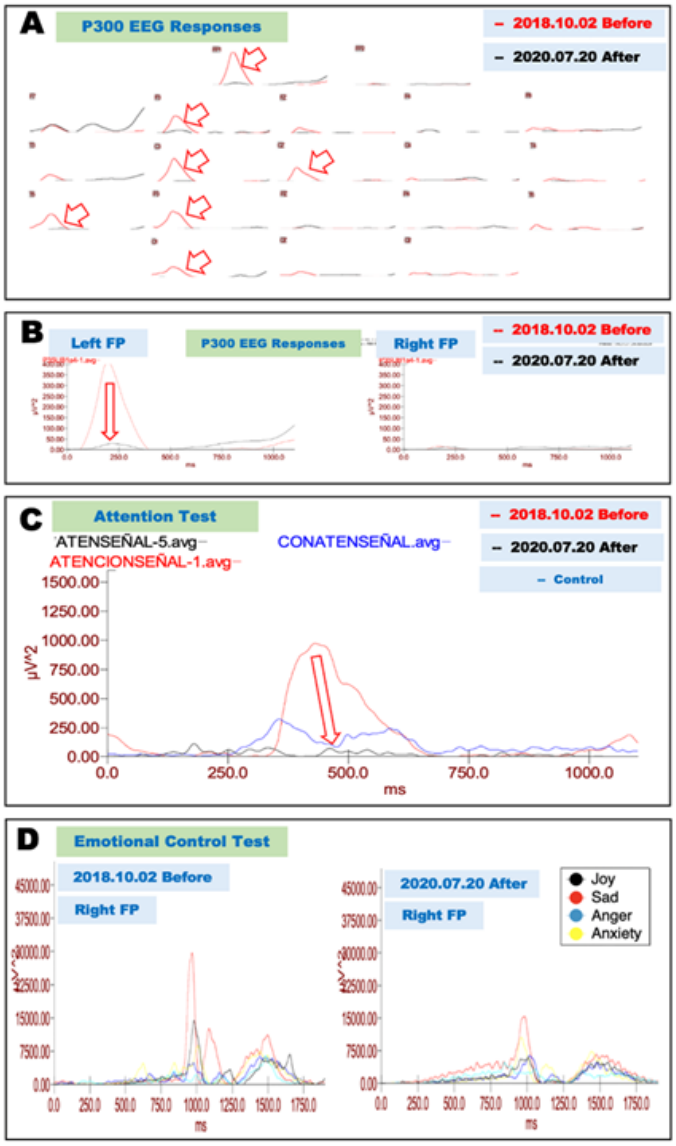

Figure 2. Neurophysiological evaluations before and after cytokine treatment.

A. Electrophysiological evaluation of P300 EEG responses before and after cytokine-induced neurogenesis. P300 EEG responses recorded on October 2, 2018, before treatment, are shown as red lines, and P300 EEG responses recorded on July 20, 2020, after treatment, are shown as black lines.

B. Magnified recordings of the frontopolar leads in Fig. 3A show that the asymmetrical P300 signal recorded on October 2, 2018 (red lines), significantly improved in both frontopolar leads recorded on July 20, 2020 (black lines; left, left frontopolar leads; right, right frontopolar leads).

C. Electrophysiological data from the attention test before and after cytokine treatment. Attention tests showed that the hyperexcitable reactions recorded on October 2, 2018 (red line), were significantly suppressed on July 20, 2020 (black line).

D. Emotional control test before and after cytokine-induced neurogenesis. Hyperexcitable reactions recorded in the right frontopolar leads on October 2, 2018, were significantly suppressed on July 20, 2020.

MRI data acquired on September 4, 2018, revealed mild atrophy of the cerebral cortex in the frontal lobes and anterior cingulate cortex (ACC) (Figure 4A). A cross-sectional cortical image showed reduced volumes of white matter with enlarged sulci in the right prefrontal cortex (Figure 3C, red arrow), posterior cortex (Figure 4C) and anterior cortex (Figure 4E). In silico endoscopic images of the left hippocampus (Figure 5A) and right hippocampus (Figure 3B) revealed moderate atrophy in the neck portions of both hippocampi (Figure 5A & 5B, red arrows). However, blood chemistry, CBC, thyroid function, autoantibodies, and HbA1c did not indicate any disorders associated with dementia or mood disorders. We therefore diagnosed the patient with bipolar disorder (BPD) based on the clinical symptoms, morphological abnormalities, and electrophysiological abnormalities, which were compatible with the brain pathology of BPD in the cerebral cortex, limbic system, and hippocampus.

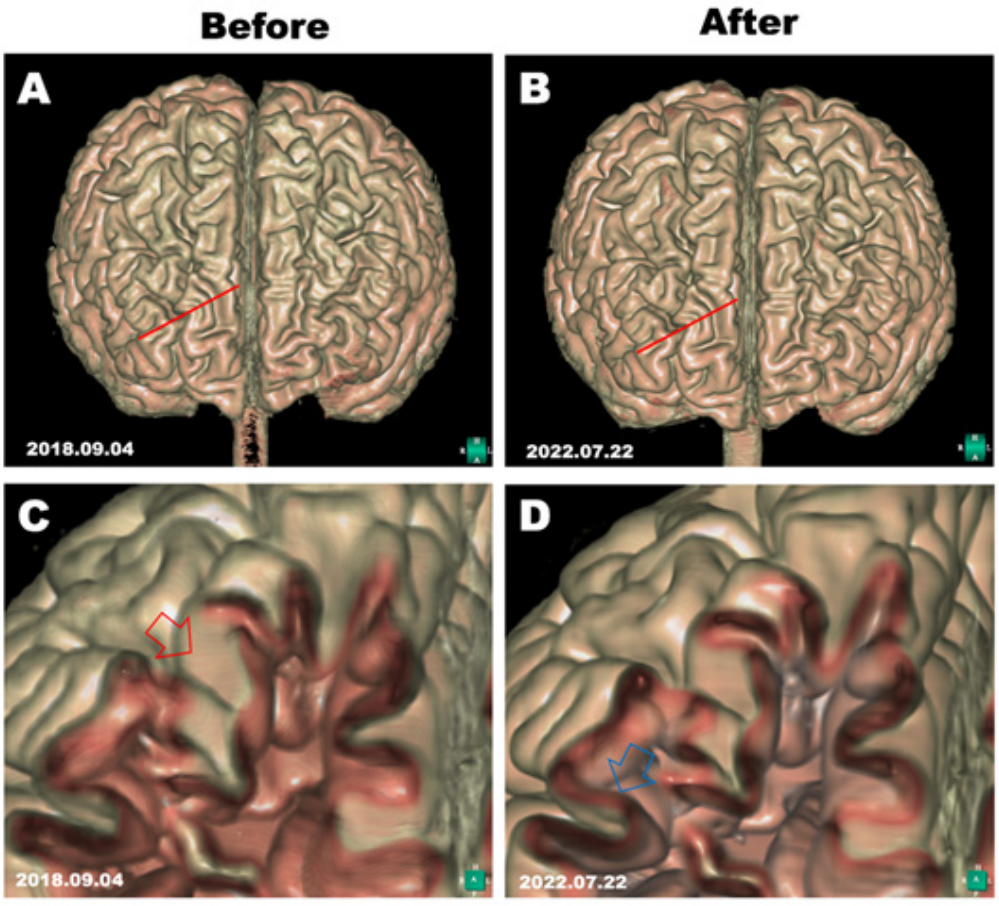

Figure 3. Morphological evaluations of the prefrontal cortex before and after cytokine-induced neurogenesis.

MRI scans on September 9, 2018, and on July 22, 2022, before and after cytokine cocktail treatment. A., B. 3D structure of the cerebral cortex (anterior view) reconstructed in silico using Expert INTAGER software from MRI T1-weighted images with 1 mm sagittal slices before and after cytokine cocktail treatment. C., D. Cut surface images of the frontal lobe as indicated by the red lines in A and B show the regeneration of the atrophied cerebral cortex. E., F. Cut surface images of the frontal lobe as indicated by the green lines in A and B show the regeneration of the atrophied cerebral cortex.

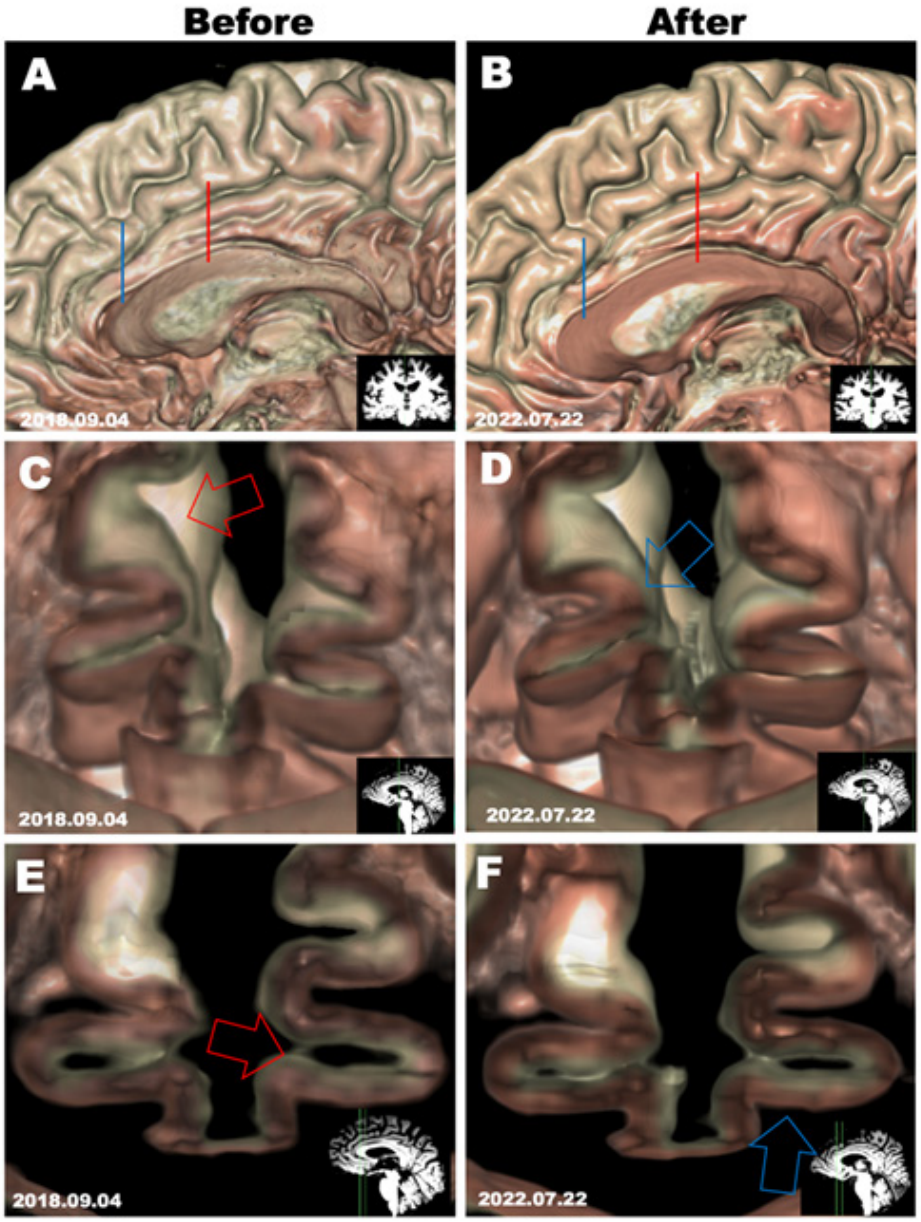

Figure 4. Morphological evaluations of the anterior cingulate cortex (ACC) before and after cytokine-induced neurogenesis.

MRI scans on September 9, 2018, and on July 22, 2022, before and after cytokine cocktail treatment. A., B. 3D structure of the ACC (sagittal view) before and after cytokine cocktail treatment. C., D. Cut surface images of the posterior ACC, as indicated by the red lines in A and B, showing the regeneration of the atrophied cerebral cortex. E., F. Cut surface images of the anterior ACC, as indicated by the blue lines in A and B, showing the regeneration of the atrophied cerebral cortex.

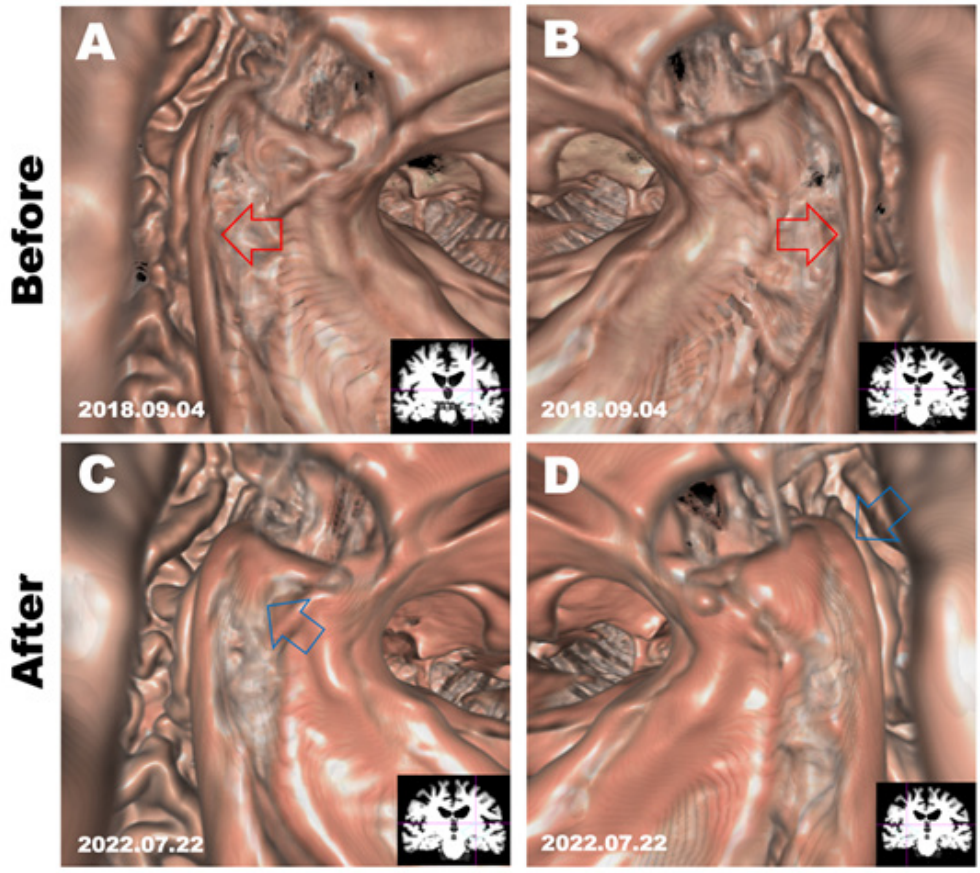

Figure 5. Morphological evaluations of the hippocampus before and after cytokine-induced neurogenesis. A., B. Endoscopic in silico images of the left hippocampus (A) and right hippocampus (B) showing atrophy at the neck portion of the hippocampus. C, D. Endoscopic in silico images of the left hippocampus (C) and right hippocampus (D) after cytokine treatment showing the regeneration of the hippocampus at the neck.

To induce neurogenesis, we therapeutically applied a cytokine cocktail: Gabatrof (EPI), Gabatrof (ADPK), and Epatrof (PSY), which contain hepatocyte growth factor (HGF), granulocyte colony stimulating factor (GCSF), adiponectin, and brain-derived neurotrophic factor (BDNF) from October 16, 2018, to July 20, 2020, as shown in Figure 1. The cytokine cocktail formulation used in this study was designed and developed by Luis Carlos Aguilar Cobos at the Livant Neurorecovery Center, Mexico, as described previously [7-11]. One year and 9 months after cytokine cocktail treatment (on July 20, 2020), we reevaluated the patient's EEG signals, which showed a significant decrease in slow waves (data not shown). An excessive P300 EEG response was significantly suppressed in the right frontopolar, right frontal, right central, right temporal, right parietal, and right occipital leads (Figure 2A, black lines), suggesting that inhibitory GABAergic neurons were regenerated to suppress the hyperexcitable P300 responses evoked by glutamatergic neuronal activity before treatment, as suggested previously [7]. Higher magnification of P300 responses in the frontal leads clearly showed that the P300 response voltage was significantly suppressed after cytokine treatment to 25 μV^2 in the left frontal leads at 240 msec (Figure 2B, black lines, left panel) and to 10 μV2 in the right frontal lead at 240 msec (Figure 2B, black lines, right panel). The attention test showed that the overreactive response observed on October 02, 2018 (Figure 2C, red line), was significantly suppressed on July 20, 2020 (Figure 2C, black line), implying that the impairment of attention was mitigated by cytokine treatment. An emotional control test, performed on July 20, 2020, showed a significant suppression of the hyperexcitability that had been observed at the right frontopolar lead on October 2, 2018 (Figure 2D, left panel), during an emotional control test with all emotions, including joy, sadness, anger, anxiety, and neglect (Figure 2D, right panel), implying that the depressed mood was also alleviated by cytokine treatment.

On July 22, 2022, we performed MRI, which revealed no marked changes in the volume of the atrophied gyri in the prefrontal cortex (Figure 3B) or the anterior cingulate cortex (ACC) (Figure 4B). The cut surface image showed a reorganization of gray matter in the prefrontal cortex (Figure 3D), posterior portion (Figure 4D), and anterior portion

(Figure 4F) of the AAC, suggesting that structural alterations were induced by cytokine treatment, as suggested previously [8]. This structural alteration may be clinically compatible with improved cognitive flexibility and executive function (Figure 1). Endoscopic in silico images of the hippocampus revealed that the previously observed atrophy was partially reversed in the neck of the left hippocampus (Figure 5C, blue arrow) and in the neck of the right hippocampus after treatment (Figure 5D, blue arrow), which is clinically compatible with the improved verbal memory observed on July 22, 2022 (Figure 1).

We followed the clinical course of emotional control for 2 years after cytokine cocktail treatment (Figure 1, Figure 6). For all emotions, including joy, sadness, anger, anxiety, and neglect, the electrophysiological responses in the left frontopolar lead recorded on July 22, 2022, showed normal emotional responses with a peak voltage less than 10,000 μV^2 (Figure 6), suggesting that GABAergic inhibitory neurons, which were regenerated by cytokine cocktail treatment from October 2, 2018, to July 20, 2020, continued to suppress emotional overreactions without further cytokine treatment (Figure 6B, 6C).

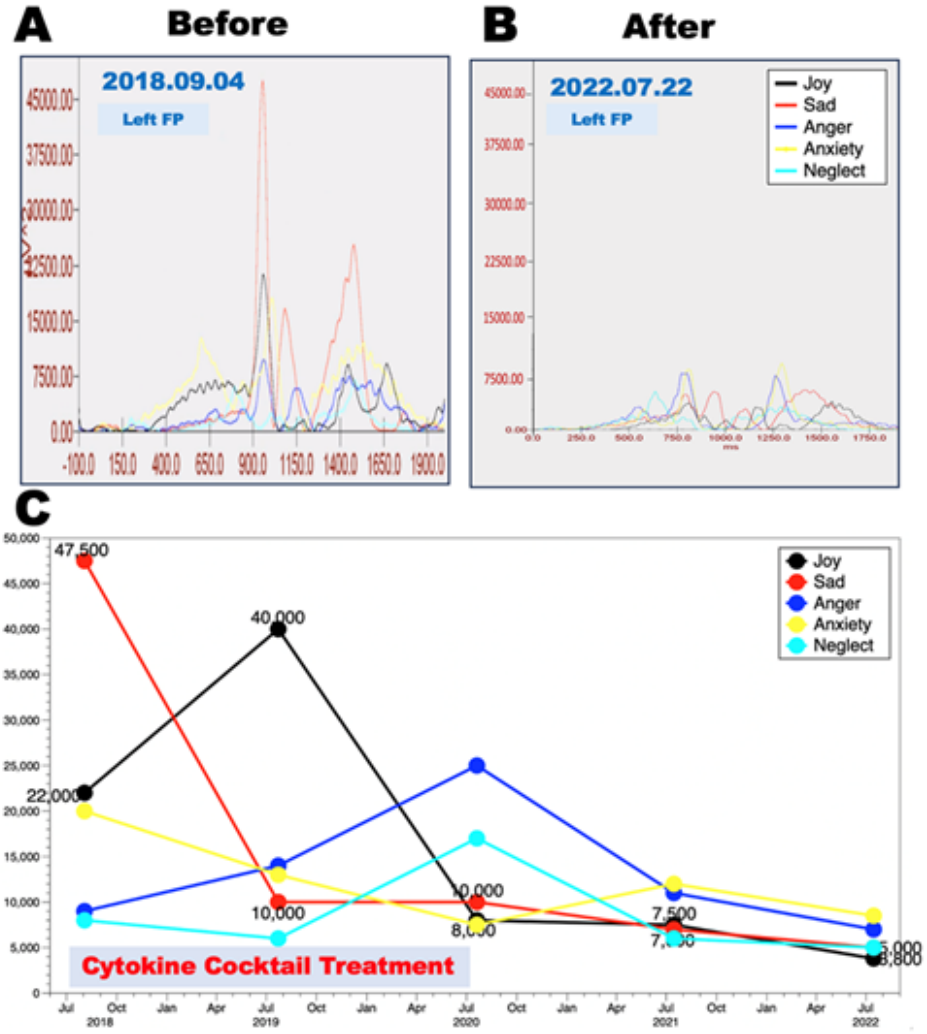

Figure 6. Neurophysiological projection of the emotional control test before and 2 years after cytokine treatment.

A., B. Hyperexcitable reactions recorded in the left frontopolar leads on October 2, 2018 (A), were significantly suppressed on July 22, 2022, 2 years after cytokine cocktail treatment (B). Emotional reactions for joy (black line), sadness (red line), anger (blue line), anxiety (yellow line), and neglect (light blue) are recorded on the left frontopolar lead.

C. Clinical course of neurophysiological evaluations for the emotional control test. Hyperexcitable reactions for sadness, joy, and anxiety were suppressed in July 2020 after 2 years of cytokine cocktail treatment, and the suppression was maintained for two years after treatment.

DISCUSSION

In the present case report, we demonstrated for the first time that cytokine-induced neurogenesis of GABAergic and glutamatergic neurons regenerated the atrophied hippocampus, prefrontal cortex, and ACC in association with clinical improvements in emotional control. Neurophysiological assessment clearly showed that cortical neural networks exhibited hyperexcitability in the left cerebral cortex in P300 EEG reactions and hyperexcitability in frontopolar leads during attention and emotional control tests (Figure 2), which were pathophysiologically compatible with BPD. Since deficits in GABAergic neurons in the cerebral cortex result in hyperexcitable glutamatergic responses during sound stimulation, attention tests, and emotional control tests, as previously described [7], the pathophysiology of BPD may be partly attributable to a deficiency in GABAergic inhibitory neurons in the cerebral cortex [8]. It is then reasonable to speculate that the neurogenesis of GABAergic neurons mitigated neurophysiological abnormalities, such as hyperexcitability in the P300 response, attention test, and emotional control test, in association with clinical improvements in depressed mood.

In the cerebral cortex, two types of GABAergic neurons are neurophysiologically defined: GABAergic interneurons, which connect locally to different neurons and harmonize excess neuronal activation by locally inhibiting specific messages, and GABAergic projection neurons, which transfer inhibitory information to other regions of the brain (Figure 7). Various types of GABAergic interneurons are localized in different shapes and properties in the layers of the cerebral cortex and are thought to play a key role in many cognitive functions, such as learning and memory [12]. Among them, 7 types of GABAergic interneurons, which mainly compose the inhibitory network surrounding the glutamatergic pyramidal cells in layers II-VI of the cerebral cortex, are illustrated in Figure 7. Therefore, GABAergic interneurons constitute the main inhibitory neural network that controls hyperexcitability in the brain [13]. Among them, PV+ basket cells and CCK+ basket cells innervate the dendrites of pyramidal cells (Figure 7B, 7C, blue) and inhibit the input signal of pyramidal cells. PV+ Chandelier cells (Figure 7B, 7C, green) innervate the axons of pyramidal cells and inhibit the output signal from pyramidal cells. Martinotti cells are small multipolar neurons with short branching dendrites (Figure 7B, 7C, dark blue). Martinotti cells are scattered throughout various layers of the cerebral cortex, sending their axons up to cortical layer II, where they undergo axonal arborization (Figure 7B, 7C, dark blue). When pyramidal neurons are overexcited, Martinotti cells start sending inhibitory signals to the surrounding neurons [13]. Neurogliaform cells (NGCs) (Figure 7B, 7C, orange) represent the main source of slow cortical inhibition by acting on metabotropic GABAB receptors [12] and are thought to be the key effector of a powerful inhibitory circuit recruited by long-range connections such as interhemispheric and thalamic projections [14,15].

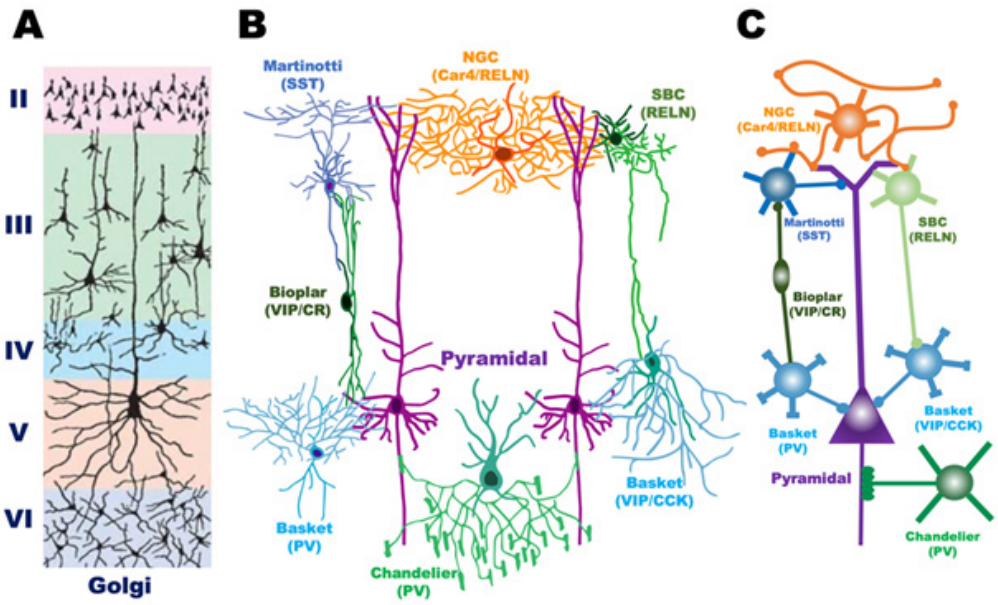

Figure 7. Pyramidal neurons and GABAergic inhibitory interneurons in the cerebral cortex.

A. Golgi staining of the cerebral cortex. The layer numbers are indicated along the vertical axis. Layers II, III, IV, V, and VI are marked with red, green blue, orange, and violet backgrounds, respectively. The figure was modified from a website (https://www.humanneurophysiology.com/cerebralcortex.htm).

B. GABAergic interneurons are classified into 7 subclasses: Martinotti somatostatin (SST) cells, parvalbumin (PV) basket cells, PV+ chandelier cells, vasointestinal peptide (VIP)/cholecystokinin (CCK) basket cells, VIP/calretinin (CR) bipolar cells, reelin (RELN) single-bouquet cells, and RELN+ neurogliaform cells (NGCs).

C. Schematic of subcellular innervations of various GABAergic interneuron types on pyramidal neurons. PV basket cells innervate the dendrites and soma of pyramidal cells. PV chandelier cells exclusively innervate the axon initial segment of pyramidal cells. VIP+ bipolar neurons commonly innervate the SST; Martinotti cells disinhibit pyramidal cells. CCK+ basket cells display a slower firing rate than PV+ basket cells. The NGC is a distinct subtype of GABAergic neuron that acts as the main effector of a powerful inhibitory motif recruited by long-range connections.

GABAergic neurons are present not only as local interneurons but also as long projection neurons in the PFC, anterior cingulate cortex (ACC), amygdala, nucleus accumbens (NAc), ventral tegmental area (VTA), and hippocampus (HPC) (Figure 8), which are functionally associated with decision-making, cognition, intelligence, memory, sleep, emotions, motivation, and pleasure [16]. GABAergic projection neurons are widely distributed throughout the brain and make dense connections between brain regions involved in mood regulation and reward learning (Figure 8) [16]. Three types of GABAergic projection neurons, which include projection neurons from the HT to the parietal cortex and frontal cortex and from the NAc to the TH and VTA, have been reported to be involved in the pathogenesis of BPD (Figure 8, blue lines) [16].

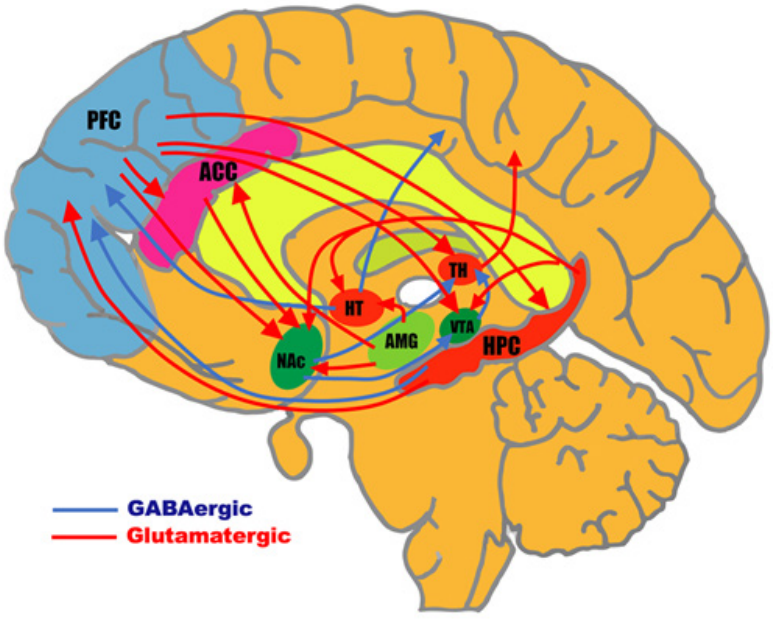

Figure 8. Glutamatergic and GABAergic projection neurons in the cerebral cortex and limbic system.

Glutamatergic projections illustrated here (as indicated by red arrows) include those from the prefrontal cortex (PFC) to the anterior cingulate cortex (ACC), thalamus (TH), ventral tegmental area (VTA), hippocampus (HPC) and nucleus accumbens (NAc); from the hippocampus to the hypothalamus (HT), VTA, NAc and PFC; and from the amygdala (AMG) to the HT. The GABAergic projection neurons illustrated here (as indicated by green arrows) include those from the HT to the parietal cortex and frontal cortex and from the NAc to the TH and VTA. Figure is reproduced from AJ. Cutler et al. 2023 [16].

The prefrontal cortex (PFC) has emerged as the region most consistently impaired in major depressive disorder (MDD) and BPD patients. Functional and structural PFC abnormalities have been reported in individuals with MDD or BPD [17]. Especially, medial prefrontal cortex (mPFC) is characterized by a decrease in volume, reductions in neuronal size, and/or changes in neuronal density, reductions in glial cell density, and changes in gene expression in postmortem examination of BPD [18]. These data suggest the presence of dendritic atrophy of neurons and the loss of oligodendroglial cells in BPD, in association with a reduction in the cell counts of specific subpopulations of GABAergic interneurons [18].

The PFC has been shown to be affected by stressors and the psychosocial environment in a human study. Severe acute stressors impair cognitive function largely via adrenergic or glucocorticoid responses [19]. Even mild acute uncontrollable stress can cause a rapid loss of prefrontal cognitive abilities, whereas more prolonged chronic stress exposure causes architectural changes in prefrontal dendrites [20]. In the present study, mild atrophy of the prefrontal cortex associated with structural disorganization of the cerebral cortex (Figure 3) was observed, which was consistent with the findings of previous studies of stress-induced depression in animal models and huma [21]. Since transcranial magnetic stimulation (TMS) to the prefrontal cortex has been reported to be a clinically effective treatment for depression [21], the PFC may play an important physiological role in emotional control and a pathological role in MDD or BPD.

A functional MRI study of BPD patients revealed that patients activated significantly fewer voxels within the cingulate cortex (CC) and more voxels within the prefrontal cortex (PFC) [22], which is associated with impaired cognitive control [22], suggesting a hyperexcitable brain pathology in the prefrontal cortex in association with an adaptive or dysregulated pathology in the cingulate cortex. This idea may not contradict the neurophysiological and morphological abnormalities observed in the present case study.

Atwood et al. reported a decreased volume of the hippocampus in baseline MRI data from a BPD cohort [23]. A longitudinal study on a BPD cohort, however, revealed significant increases in the anterior hippocampal region and dentate gyrus volume in BPD patients compared with controls [23]. Interestingly, antipsychotic medication use was positively correlated with the volume of the posterior region of the hippocampus. These findings highlight the brain plasticity of BPD patients, providing evidence that hippocampal volume is associated with adaptive responses to atypical hyperexcitability rather than progressive degeneration. In the present study, the head (anterior part) of the hippocampus was well preserved, while the neck (posterior part) of the hippocampus was degenerated according to MRI (Figure 5). Furthermore, the neck region of the hippocampus was regenerated after cytokine cocktail treatment (Figure 5), confirming the previous hypothesis that the hippocampus adaptively responds to atypical hyperexcitable neuronal inputs due to BPD.

In the present study, we used a cytokine cocktail that contained HGF, GCSF, adiponectin, and BDNF (Figure 1). Hepatocyte growth factor (HGF) and its tyrosine kinase receptor, encoded by the MET cellular proto-oncogene, are expressed in the nervous system from prenatal development to adult life, where they are involved in neuronal growth and survival [24]. HGF-induced MET activation also exerts beneficial neuroprotective effects in adulthood, specifically in neurodegenerative diseases [7], and in preclinical models of cerebral ischemia, spinal cord injuries, and neurological pathologies, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). HGF is a key factor that prevents neuronal death and promotes survival through proangiogenic, anti-inflammatory, and immunomodulatory mechanisms. Recent evidence also suggested that HGF acts on neural stem cells to enhance neuroregeneration [24]. Interestingly, astrocyte mediated HGF/SF (scatter factor) supplementation restored GABAergic interneurons and improved learning deficits in mice [25]. Furthermore, MET promoter variant rs1858830 signaling appears to contribute to gastrointestinal abnormalities associated with autism spectrum disorder (ASD) [26]. The rs1858830 MET promoter variant is also predictive of atypical fMRI activation and deactivation patterns in the human brain in response to social stimuli [27], suggesting that HGF-MET signaling in the cerebral cortex may play an important role in the pathogenesis of emotion disorders.

Granulocyte colony-stimulating factor (G-CSF), a member of the hematopoietic growth factor family, is also critically involved in controlling the proliferation and differentiation of neural stem cells [28]. Treatment with G-CSF has been shown to result in substantial neuroprotective and neuroregenerative effects in various experimental models of acute and chronic diseases of the central nervous system [28]. Although G-CSF has been tested in a clinical study for the treatment of acute ischemic stroke, there are only fragmentary data on the distribution of this cytokine and its receptor in the human brain [28]. While G-CSF has been shown to exert neuroprotective effects in animal models of Alzheimer's disease (AD), we have recently shown the clinical application of G-CSF for the treatment of AD, with a reversal of cognitive functions [7].

Adiponectin (ADPN) is a plasma protein secreted by adipose tissue that has pleiotropic antidiabetic, anti-atherogenic, and anti-inflammatory effects. Initially, it was thought that the main role of adiponectin was only metabolism control. Later, ADPN receptors were also found in the central nervous system (CNS) [29]. In fact, the receptors AdipoR1 and AdipoR2 are expressed in various areas of the brain, including the hypothalamus, hippocampus, and cortex [29]. While AdipoR1 regulates insulin sensitivity through the activation of the AMP-activated protein kinase (AMPK) pathway, AdipoR2 stimulates neural plasticity through the activation of the peroxisome proliferator-activated receptor alpha (PPARα) pathway, which inhibits inflammation and oxidative stress. Overall, based on its central and peripheral actions, ADPN appears to have neuroprotective effects by

reducing inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL6), and tumor necrosis factor alpha (TNF-alpha) [30]. In addition, ADPN appears to have insulin-sensitizing effects. A reduction in insulin signaling is known to be associated with cognitive impairment. Therefore, it is of great interest to investigate the mechanism of restoration of insulin signaling in the brain as an action of ADPN [30]. However, ADPN has not yet been reported for clinical application for BPD, so this is the first case report in which ADPN was applied to control emotional abnormalities due to BPD.

Brain-derived neurotrophic factor (BDNF) plays an important role in a variety of neuronal processes, such as differentiation, maturation, and synaptic function in the central nervous system (CNS) [31]. BDNF stimulates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphoinositide-3 kinase (PI3K), and phospholipase C (PLC)-gamma pathways via activation of tropomyosin receptor kinase B (TrkB), a high-affinity receptor for BDNF [31]. In vivo and in vitro studies have shown the significant contributions of these signaling pathways to neurogenesis and synaptic plasticity. Importantly, dysfunction of the BDNF/TrkB system is involved in the onset of brain diseases, including neurodegenerative disorders such as Alzheimer's disease and psychiatric disorders such as BPD. Many neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are associated with the pathogenesis of mood disorders [32]. This is the first case report in which BDNF combined with HGF, G-CSF, and ADPN was applied to treat BPD. Several studies have shown that BDNF may be indispensable for the neuroimmune regulation of mood disorders. Since the potential mechanism by which BDNF affects mood disorders has not been elucidated [33], further studies are needed to clarify the basic biological mechanisms of action of cytokine cocktail treatment for BPD.

CONCLUSION

Bipolar disorder (BPD) is a mental health condition that causes extreme mood swings for which specific brain pathology has not yet been precisely defined. In the present study, we administered cytokine-induced neurogenesis treatment to a 60-year-old male BPD patient to regenerate GABAergic neurons as well as glutamatergic neurons, which resulted in a successful regeneration of the atrophied hippocampus and disorganized cortical structures of the prefrontal cortex and ACC, which was associated with improved emotional control and the resolution of electrophysiological abnormalities. To the best of our knowledge, this is the first case report demonstrating that cytokine-induced GABAergic and glutamatergic neurogenesis repairs brain pathology due to BPD and improves emotional control.

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ETHICAL APPROVAL OF STUDIES AND INFORMED CONSENT

Written informed consent was obtained from the patient.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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