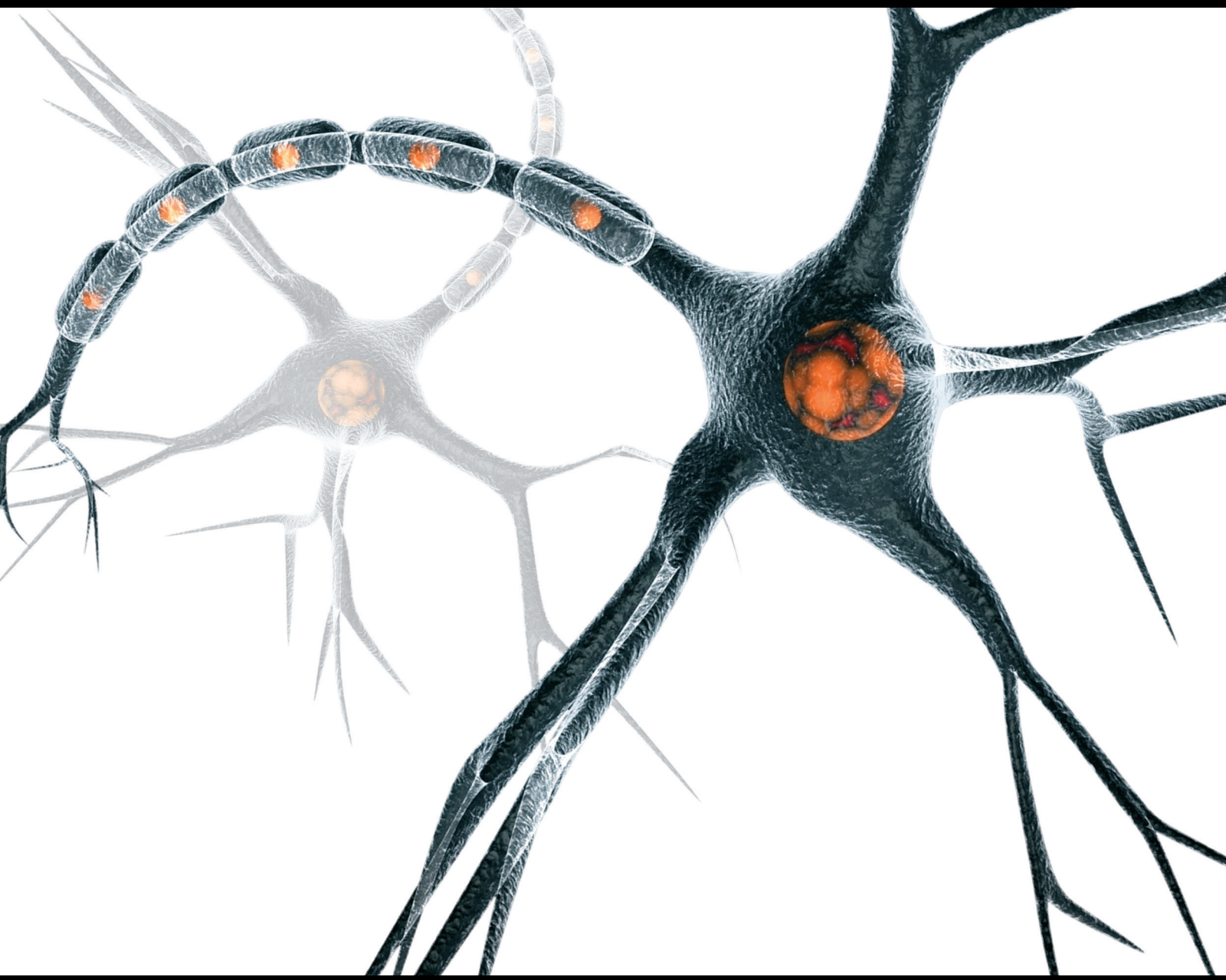
Neural Plasticity

Synaptic Plasticity Changes: Hallmark for Neurological and Psychiatric Disorders

Lead Guest Editor: Giuseppina Martella
Guest Editors: Paola Bonsi, Steven W. Johnson, and Angelo Quartarone



Synaptic Plasticity Changes: Hallmark for Neurological and Psychiatric Disorders

Neural Plasticity

Synaptic Plasticity Changes: Hallmark for Neurological and Psychiatric Disorders

Lead Guest Editor: Giuseppina Martella
Guest Editors: Paola Bonsi, Steven W. Johnson, and Angelo Quartarone

Editorial Board

Contents

Hindawi
Neural Plasticity
Volume 2018, Article ID 9230704, 3 pages
https://doi.org/10.1155/2018/9230704

Editorial

Synaptic Plasticity Changes: Hallmark for Neurological and Psychiatric Disorders

Giuseppina Martella,[1] **Paola Bonsi**,[2] **Steven W. Johnson**,[3] **and Angelo Quartarone**[4]

[1]*University of Rome Tor Vergata, Rome, Italy*
[2]*IRCCS Fondazione Santa Lucia, Rome, Italy*
[3]*Oregon Health & Science University, Portland, USA*
[4]*University of Messina, Messina, Italy*

Correspondence should be addressed to Giuseppina Martella; martella@med.uniroma2.it

Received 17 September 2018; Accepted 17 September 2018; Published 21 October 2018

Many molecular mechanisms cooperate to produce synaptic plasticity changes. These include alterations in neurotransmitter release and in the effectiveness of neuronal response to those neurotransmitters. Defining and understanding how these mechanisms are involved in neuropathological conditions are a major challenge for neuroscience in the third millennium.

Indeed, synaptic dysfunction is involved in a great number of neurological conditions, such as neurodegenerative diseases (Alzheimer's, Parkinson's, and Huntington's disease), dystonia, levodopa-induced dyskinesia, and ischemia [1–8], as well as neuropsychiatric conditions such as autism, schizophrenia, and major depression [9–15]. Moreover, synaptic plasticity alterations can appear in an early asymptomatic phase of the disease [16, 17].

Therefore, the aim of this special issue is to highlight synaptic plasticity changes as a hallmark of neurological and neuropsychiatric diseases.

In this issue, M. Cantone et al. report altered mechanisms of neural plasticity associated with long-term hand motor deficits in adult patients with intellectual disability. Intellectual disability is commonly associated with impairments in psychomotor skills and abilities of daily living. These authors studied the effects of a two-month program of hand-motor rehabilitation and visual-perceptual treatment in a population of 30 subjects with mild intellectual impairment. The study reports that this group had significantly better motor performance compared to an intellectually impaired group that received conventional rehabilitation. These results suggest that a program that emphasizes visual-perceptual and motor skills may be superior to conventional rehabilitation in improving motor function in the mildly intellectually impaired individuals. From a neuroanatomical perspective, motor learning requires the development and retention of several skills, depending on the structural and functional integrity of the neostriatum and the cerebellum. These brain structures are considered the substrate of learning and memory, both in development and aging and in physiological and pathological conditions [18]. The findings from this report open new exciting windows on the non-invasive rehabilitative interventions targeting the cortical plasticity and neural connectivity.

C, Terranova et al. investigated the mechanism contributing to the selection of voluntary movements in focal hand dystonia, a syndrome characterized by muscle spasms giving rise to involuntary movements and abnormal postures. Significant alterations in synaptic plasticity were described in dystonic animal models as well as in patients [6, 19–22]. In the present work, the authors evaluated the spatial and temporal somatosensory integration by recording somatosensory evoked potentials (SEPs) in controls and patients with focal dystonia. Patients usually present two main abnormalities:

greater facilitation and loss of spatial specificity. Here, the authors demonstrated that the inhibitory integration of somatosensory inputs in focal hand dystonia is normal during sensory-motor plasticity.

J. E. Orfila et al. used a model of cardiac arrest and cardiopulmonary resuscitation (CA/CPR) to produce global brain ischemia and assess whether ischemic LTP (a pathological form of synaptic plasticity induced in acute brain slices by oxygen and glucose deprivation) is reproduced *in vivo*. Indeed, the authors found an increased postsynaptic glutamate receptor phosphorylation and function and a preserved ability to depotentiate CA1 synapses. Ischemic LTP was found to occlude physiological LTP, providing a possible target for interventional strategies to improve memory function after cardiac arrest. This is the first study to demonstrate that *in vivo* ischemia causes synaptic alterations that are consistent with ischemic LTP and represent a new model to characterize aberrant forms of synaptic plasticity.

In the last section of this issue, three reviews point to the attention on the molecular mechanisms underlying synaptic plasticity alterations.

U. Shefa et al. discuss the role of diffusible gaseous transmitters (gasotransmitters) in regulating neuronal excitability and plasticity. In this review, the authors summarize recent evidence on the role of hydrogen sulfide, nitric oxide, and carbon monoxide in synaptic plasticity, emphasizing that these gaseous neurotransmitters can play roles in neurological conditions such as schizophrenia, bipolar disorder, major depressive disorder, and Alzheimer's disease. They suggest that rescuing homeostatic levels of gasotransmitters may restore synaptic plasticity and proper neuronal functioning.

P. Olivero et al. perform a thorough analysis of the role of mitochondria in synaptic alterations underlying psychiatric and neurodegenerative disorders. The efficiency of the cellular physiological processes is governed by an appropriate protein localization and function. A molecular network, called the proteostasis network, participates in the intricate mechanisms of synthesis, folding, trafficking, and degradation necessary to ensure the structure and function of proteins. Dysfunction of the proteostatic network affects neuronal plasticity, and the authors discuss the role of some proteins involved in common diseases, in plasticity alteration and neurodegeneration.

The inflammatory cytokines tumor necrosis factor (TNF) and interleukin-1β (IL-1β) play important physiological roles in LTP and synaptic scaling. However, actions of these cytokines on synaptic plasticity can be altered under conditions of neuroinflammation. F. R. Rizzo et al. provide a timely summary of the important effects of inflammatory cytokines on synaptic plasticity in health and disease and discuss the role of TNF and IL-1β in synaptic plasticity under either physiological or inflammatory conditions, with special emphasis on experimental allergic encephalitis and multiple sclerosis.

The contributions collected in the present issue show the importance of correct synaptic adaptations in the maintenance of a physiological state. Overall, these works show that indeed synaptic plasticity changes may represent a hallmark for neurological and psychiatric disorders.

Conflicts of Interest

All the authors declare that no competing financial interests exist.

Giuseppina Martella
Paola Bonsi
Steven W. Johnson
Angelo Quartarone

References

[1] A. Quartarone, J. Classen, F. Morgante, K. Rosenkranz, and M. Hallett, "Consensus paper: use of transcranial magnetic stimulation to probe motor cortex plasticity in dystonia and levodopa-induced dyskinesia," *Brain Stimulation*, vol. 2, no. 2, pp. 108–117, 2009.

[2] L. A. Raymond, "Striatal synaptic dysfunction and altered calcium regulation in Huntington disease," *Biochemical and Biophysical Research Communications*, vol. 483, no. 4, pp. 1051–1062, 2017.

[3] P. Calabresi, A. Pisani, J. Rothwell, V. Ghiglieri, J. A. Obeso, and B. Picconi, "Hyperkinetic disorders and loss of synaptic downscaling," *Nature Neuroscience*, vol. 19, no. 7, pp. 868–875, 2016.

[4] T. Schirinzi, G. Madeo, G. Martella et al., "Early synaptic dysfunction in Parkinson's disease: insights from animal models," *Movement Disorders*, vol. 31, no. 6, pp. 802–813, 2016.

[5] A. Stefani, E. Olivola, M. Bassi et al., "Strength and weaknesses of cerebrospinal fluid biomarkers in Alzheimer's disease and possible detection of overlaps with frailty process," *CNS & Neurological Disorders Drug Targets*, vol. 12, no. 4, pp. 538–546, 2013.

[6] G. Martella, A. Tassone, G. Sciamanna et al., "Impairment of bidirectional synaptic plasticity in the striatum of a mouse model of DYT1 dystonia: role of endogenous acetylcholine," *Brain*, vol. 132, no. 9, pp. 2336–2349, 2009.

[7] P. Calabresi, E. Saulle, D. Centonze, A. Pisani, G. A. Marfia, and G. Bernardi, "Post-ischaemic long-term synaptic potentiation in the striatum: a putative mechanism for cell type-specific vulnerability," *Brain*, vol. 125, no. 4, pp. 844–860, 2002.

[8] P. Calabresi, D. Centonze, A. Pisani, L. M. Cupini, and G. Bernardi, "Synaptic plasticity in the ischaemic brain," *Lancet Neurology*, vol. 2, no. 10, pp. 622–629, 2003.

[9] C. Hansel, "Deregulation of synaptic plasticity in autism," *Neuroscience Letters*, 2018.

[10] E. Nanou and W. A. Catterall, "Calcium channels, synaptic plasticity, and neuropsychiatric disease," *Neuron*, vol. 98, no. 3, pp. 466–481, 2018.

[11] Y. Sattar, J. Wilson, A. M. Khan et al., "A review of the mechanism of antagonism of N-methyl-D-aspartate receptor by ketamine in treatment-resistant depression," *Cureus*, vol. 10, no. 5, article e2652, 2018.

[12] G. Martella, M. Meringolo, L. Trobiani, A. De Jaco, A. Pisani, and P. Bonsi, "The neurobiological bases of autism spectrum disorders: the R451C-neuroligin 3 mutation hampers the expression of long-term synaptic depression in the dorsal striatum," *The European Journal of Neuroscience*, vol. 47, no. 6, pp. 701–708, 2018.

[13] F. E. Henry, W. Hockeimer, A. Chen, S. P. Mysore, and M. A. Sutton, "Mechanistic target of rapamycin is necessary for changes in dendritic spine morphology associated with long-term potentiation," *Molecular Brain*, vol. 10, no. 1, p. 50, 2017.

[14] E. Santini, T. N. Huynh, A. F. MacAskill et al., "Exaggerated translation causes synaptic and behavioural aberrations associated with autism," *Nature*, vol. 493, no. 7432, pp. 411–415, 2013.

[15] N. H. Jung, W. G. Janzarik, I. Delvendahl et al., "Impaired induction of long-term potentiation-like plasticity in patients with high-functioning autism and Asperger syndrome," *Developmental Medicine and Child Neurology*, vol. 55, no. 1, pp. 83–89, 2013.

[16] G. Madeo, T. Schirinzi, G. Martella et al., "*PINK1* heterozygous mutations induce subtle alterations in dopamine-dependent synaptic plasticity," *Movement Disorders*, vol. 29, no. 1, pp. 41–53, 2014.

[17] E.-K. Tan, F. S. Refai, M. Siddique et al., "Clinically reported heterozygous mutations in the PINK1 kinase domain exert a gene dosage effect," *Human Mutation*, vol. 30, no. 11, pp. 1551–1557, 2009.

[18] J. D. Sweatt, "The emerging field of neuroepigenetics," *Neuron*, vol. 80, no. 3, pp. 624–632, 2013.

[19] M. Maltese, J. Stanic, A. Tassone et al., "Early structural and functional plasticity alterations in a susceptibility period of DYT1 dystonia mouse striatum," *eLife*, vol. 7, 2018.

[20] G. Martella, M. Maltese, R. Nisticò et al., "Regional specificity of synaptic plasticity deficits in a knock-in mouse model of DYT1 dystonia," *Neurobiology of Disease*, vol. 65, pp. 124–132, 2014.

[21] A. Quartarone and A. Pisani, "Abnormal plasticity in dystonia: disruption of synaptic homeostasis," *Neurobiology of Disease*, vol. 42, no. 2, pp. 162–170, 2011.

[22] A. Quartarone, V. Rizzo, C. Terranova et al., "Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia," *Brain*, vol. 132, no. 10, pp. 2871–2877, 2009.

Hindawi
Neural Plasticity
Volume 2018, Article ID 4135708, 7 pages
https://doi.org/10.1155/2018/4135708

Research Article

Spatial Integration of Somatosensory Inputs during Sensory-Motor Plasticity Phenomena Is Normal in Focal Hand Dystonia

C. Terranova[1], **V. Rizzo**[1], **F. Morgante**[1], **R. Maggio**[2], **A. Calamuneri**[3], **G. Chillemi**[3], **P. Girlanda**[1] **and A. Quartarone**[3,4]

[1]*Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*
[2]*Department of Neurology, Humanitas Research Hospital, Rozzano, Milan, Italy*
[3]*IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Italy*
[4]*Department of Biomedical, Dental Science and Morphological and Functional Images, University of Messina, Italy*

Correspondence should be addressed to C. Terranova; carmen.terranova@gmail.com and V. Rizzo; enzo.rizzo@gmail.com

Received 10 February 2018; Revised 18 July 2018; Accepted 29 August 2018; Published 10 October 2018

Academic Editor: Gabriela Delevati Colpo

Background. Surround inhibition is a system that sharpens sensation by creating an inhibitory zone around the central core of activation. In the motor system, this mechanism probably contributes to the selection of voluntary movements, and it seems to be lost in dystonia. *Objectives.* To explore if sensory information is abnormally processed and integrated in focal hand dystonia (FHD) and if surround inhibition phenomena are operating during sensory-motor plasticity and somatosensory integration in normal humans and in patients with FHD. *Methods.* We looked at the MEP facilitation obtained after 5 Hz repetitive paired associative stimulation of median (PAS M), ulnar (PAS U), and median + ulnar nerve (PAS MU) stimulation in 8 normal subjects and 8 FHD. We evaluated the ratio MU/(M + U) ∗ 100 and the spatial and temporal somatosensory integration recording the somatosensory evoked potentials (SEPs) evoked by a dual nerve input. *Results.* FHD had two main abnormalities: first, the amount of facilitation was larger than normal subjects; second, the spatial specificity was lost. The MU/(M + U) ∗ 100 ratio was similar in healthy subjects and in FHD patients, and the somatosensory integration was normal in this subset of patients. *Conclusions.* The inhibitory integration of somatosensory inputs and the somatosensory inhibition are normal in patients with focal dystonia as well as lateral surrounding inhibition phenomena during sensory-motor plasticity in FHD.

1. Introduction

Dystonia is a motor disorder characterized by sustained involuntary muscular contractions resulting from cocontraction of antagonistic muscles and overflow into extraneous muscles [1]. Focal hand dystonia frequently develops after repetitive movements in the presence of overtraining. These clinical observations have pointed out toward the presence of subtle abnormalities of plasticity, within somatosensory system, which may predispose individual to dystonia after excessive training [2]. Surround inhibition is a physiological mechanism to focus neuronal activity and to select appropriate neuronal responses and has been proposed to be an essential mechanism in the motor system, to sharp and focus motor activation [3, 4]. Surround inhibition (SI) can be tested in the motor system using TMS, and it has been demonstrated that this mechanism is deranged in patients with FHD [3].

In addition, it is well known that dystonia is characterized by a defective somatosensory processing within the somatosensory system [5] associated with a disturbance of sensorimotor integration [6–8]. Indeed, proprioceptive inputs coming from adjacent body parts are abnormally integrated in dystonia. This aberrant spatial gating, probably caused by an altered lateral surrounding inhibition, could contribute to the motor impairment present in dystonia [5]. Abnormalities of inhibition within the somatosensory system have been reported by Frasson et al. [9].

Several stimulation protocols can be used to test, noninvasively, plasticity within the somatosensory motor system. One of the most established protocols is the paired associative stimulation (PAS) where a magnetic stimulus is coupled with contralateral peripheral nerve stimulation [10]. This protocol exploits the principles of Hebbian LTP/LTD plasticity first described in animal experimentation. Patients with focal hand dystonia present two main alterations after PAS: first, the amount of facilitation is larger than normal; second and more important, the spatial specificity is lost so that facilitation also occurred in surrounding muscles [11]. PAS topographical specificity is probably related to inhibitory phenomena within motor cortex and is not related to a dual nerve simultaneously stimulation.

We have characterized a new conditioning fast PAS protocol that requires only two minutes of induction called 5 Hz rPAS [12] which produces plastic changes within both excitatory and inhibitory circuits within the sensory-motor cortex.

The aim of the present study was to evaluate the spatial integration of somatosensory inputs during sensory-motor plasticity phenomena, evaluated with 5 Hz rPAS, in healthy subjects and in patients with focal hand dystonia. To achieve this goal, we compared the amplitude of MEPs obtained after the 5 Hz rPAS protocol induced by stimulating the median and ulnar nerves simultaneously (MU) vs the MEP amplitude values being obtained from the arithmetic sum of the 5 Hz rPAS protocol elicited by stimulating the same nerves separately (M + U), looking at the amount of suppression induced by dual nerve simultaneously stimulation. Moreover, we evaluated the spatial and temporal somatosensory integration recording the somatosensory evoked potentials (SEPs) evoked by a dual nerve input to investigate the contribution of lateral inhibition in the somatosensory system. Indeed, previously, Tinazzi and coworkers proposed the MU/(M + U) ∗ 100 as a marker of lateral surround inhibition evoked by a dual input in the somatosensory system [5]. In that study, the increased ratio of SEP component elicited by median + ulnar stimulation indicated an abnormality of the intrinsic inhibitory interactions within the somatosensory system and hence a defect of lateral surround inhibition.

2. Materials and Methods

Eight patients with focal hand dystonia (6 male, 2 female, mean age 50.2 years) and 8 age- and sex-matched healthy subjects were recruited (see Table 1). Writer's cramp was classified as "simple" if dystonic features were present only with writing and as "dystonic" if muscle cramps also interfered with other motor tasks [13]. Participants did not receive any drug acting on the central nervous system and had no obvious history of neuropsychiatric diseases. All patients were tested at least 3 months after the last injections of botulinum toxin. All patients had normal structural MRI scans and did not show any mutation in the DYT1 gene. All subjects were right-handed according to the Edinburgh inventory. All subjects gave their informed consent, and the study was approved by the local ethics committee in accordance with the Declaration of Helsinki on the use of human subjects in experiments.

2.1. TMS and Recording Protocol. TMS was performed with a standard focal coil (mean loop diameter of 9 cm, Magstim Company, Whitland, Dyfed, UK). The coil was placed tangentially to the scalp at the optimum scalp position which consistently elicited the best motor evoked potentials (MEPs) in the right abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles ("motor hot spot").

2.2. Median and Ulnar Nerve Stimulation. Mixed electrical stimulation of the right median and ulnar nerves was performed at the wrist with the cathode located proximally. Peripheral stimulation was performed using a Digitimer D 160 stimulator (Digitimer, Welwyn Garden City, Herts, UK). The stimulus intensity was 200% of the perceptual threshold and the stimulus width 500 μs.

2.3. Recording System. EMG was recorded from Ag-AgCl surface electrodes placed over the right abductor pollicis brevis (APB) and the right abductor digiti minimi (ADM) muscles using a belly-tendon montage. The signal was amplified and bandpass filtered (32 Hz to 1 KHz) by a DIGITIMER D 150 amplifier (Digitimer Ltd., Welwyn Garden City, Herts, UK) and stored at a sampling rate of 10 KHz (SigAvg Software, Cambridge Electronic Design, Cambridge, UK). EMG activity was continuously monitored, and trials in which the target will be not relaxed were excluded from analysis.

2.4. 5 Hz rPAS. The protocol consisted of 600 pairs of stimuli delivered at a rate of 5 Hz for two minutes. Each pair of stimuli included electrical peripheral nerve stimulation (CS) at 200% of the sensory threshold coupled with TMS at 90% active motor threshold over the motor hot spot. We take care of using always subthreshold intensities to avoid any muscle twitches produced by reafferent feedback during rPAS conditioning. The interstimulus interval (ISI) between the peripheral CS and the transcranial stimulus was fixed at 25 ms. Patients and controls received three different type of rPAS: rPAS median, rPAS ulnar, and rPAS median + ulnar. During MU rPAS, the stimulation site in the cortex was on the APB hotspot. The 5 Hz rPAS sessions were given in a random order, at least 1 week apart.

2.5. Measures of Cortical Excitability. We carefully monitored changes in cortical excitability after rPAS using single-pulse and paired-pulse TMS. The details of these techniques are given elsewhere. Several cortical excitatory parameters were taken into account before and after rPAS such as Resting Motor Threshold (RMT) and peak-to-peak MEP amplitude at rest. Measurements were acquired before 5 Hz rPAS (baseline), immediately after (T0), 15 minutes (T15), and 30 minutes (T30) after the end of the conditioning protocol. RMT is a well-standardized measure defined as the minimum intensity that could evoke a peak-to-peak MEP of 50 μV in at least 5 out of 10 consecutive trials in the relaxed APB and ADM muscles [14]. In addition, we assess corticospinal excitability by collecting 20 consecutive MEPs from the motor hot spot of the APB and ADM muscles at a rate of

Table 1: Clinical features.

Subjects	Age	Sex	Clinical features	Last botulinum toxin injection (months)	Patterns
1	50	M	Simple cramp	—	Predominant extensor pattern
2	55	M	Simple cramp	—	Predominant extensor pattern
3	31	F	Simple cramp	—	Predominant flexion pattern
4	62	M	Dystonic cramp	4	Predominant flexion pattern
5	38	M	Dystonic cramp	—	Predominant extensor pattern
6	66	M	Dystonic cramp	3	Predominant extensor pattern
7	55	F	Simple cramp	—	Predominant flexion pattern
8	45	M	Simple cramp	—	Predominant extensor pattern

0.1 Hz. We tuned and adjusted the intensity of stimulation to obtain a MEP of ~1 mV in the target muscle. This intensity was kept constant throughout the experiment. In addition, for each muscle (APB and ADM), we evaluated the ratio MU/(M + U) ∗ 100, where MU is the MEP facilitation obtained after PAS with simultaneous stimulation of median and ulnar and M + U is the amount of MEP facilitation after PAS induced after stimulation of the individual nerves.

2.6. SEP Recording Procedure. SEP studies were conducted in a different day session in order not to interfere with PAS aftereffects. SEPs were obtained after stimulation of the median and the ulnar nerves at the wrist. Stimulation parameters were square pulses of 0.2 ms duration delivered at a rate of 2.2 Hz through Ag/AgCl surface electrodes (cathode proximal; impedance below 5 Kohm) over the nerve. Further details are reported elsewhere [5, 9]. Two different sessions were carried out. In the first session, where we assessed temporal somatosensory integration, the median nerve was stimulated with single stimuli (S1) and with paired stimuli (S1 + S2) at interstimulus intervals (ISIs) of 20 and 40 ms given in a random order. S2 (test stimulus) was obtained subtracting the S1 (control response) from the S1 + S2 (paired response). In the second session, where we examined spatial somatosensory integration, the median (M) and the ulnar (U) nerves were stimulated individually and simultaneously (MU). We averaged three hundred sweeps for each trial. Analysis time was fixed at 100 ms, and filtering bandwidth was set at 5–1500 Hz. SEPs were acquired using a Signal Software (Cambridge Electronic Design, Cambridge, UK). Cortical evoked response (N20) was derived from the parietal P3 scalp regions contralateral to the stimulation side and referred to the earlobe of the stimulated side. We measured peak-to-peak amplitudes and latencies at the peak of all SEPs. For the first session, we evaluated SEP amplitudes of control (S1) and test (S2) response and the amplitude ratio (S2/S1) ∗ 100 at 20 and 40 ms of ISIs. For the second session, we evaluated the ratio MU/(M + U) ∗ 100, where MU is the SEP amplitude produced from the concomitant stimulation of median and ulnar nerves, while M + U is the arithmetic sum of the SEPs originated by the stimulation of single nerve (For more details, see [5] and [9]).

2.7. Data Analysis. The effects of 5 Hz rPAS on RMT and peak-to-peak MEP amplitude were tested in separate repeated measure analysis of variance (ANOVA). For each dependent variable, we run a three-way repeated measure ANOVA with time (two levels: baseline and post), conditioning (three levels: PAS M, PAS U, and PAS MU) as within subject factor, and group (two levels: dystonia versus controls) as between subject factor. Conditional on a significant P value, post hoc t-tests were performed to investigate the strength of main effects and the patterns of interaction between factors. To evaluate the difference in the amount of surround inhibition after rPAS between focal dystonia and controls, we performed a factorial ANOVA. Moreover, to evaluate differences in SEP amplitude between dystonic patients and controls, we used the unpaired Mann Whitney U test.

A P value of <0.05 was considered significant. Data are given as mean ± standard error of the mean.

3. Results

5 Hz rPAS did not affect RMT either in controls or in dystonic patients as indexed by no effect of the factor time and group and intervention. Figures 1 and 2 plot differences in the amount of MEP facilitation, after 5 Hz rPAS, for the APB and ADM muscles, respectively, in patients and controls. 5 Hz rPAS increased MEP size recorded from APB muscle in both patients and controls; repeated measure ANOVA disclosed a significant effect of time [$F = 88.38$; $P < 0.001$], but the amount of facilitation was different between the two groups, as revealed by the time × group interaction [$F = 21.14$; $P < 0.001$]. This effect was produced by a larger increase in MEP amplitude in dystonic patients compared to controls. We found no time × group × conditioning interaction because all the three types of intervention induced an increase in MEP amplitude in both dystonic patients and controls [$F = 1.51$; $P = 0.229$] (Figure 1). Post hoc t-test revealed that in dystonic patients all the three types of intervention induced a significant increase in MEP amplitude [PAS M: $t = -8.08$, $P < 0.001$; PAS U: $t = -5.1$, $P = 0.003$; and PAS MU: $t = -4.6$, $P = 0.007$]. On the contrary, in controls, only PAS M and PAS MU induced changes in MEP amplitude but not PAS U [PAS M: $t = -3.6$, $P = 0.008$; PAS U: $t = 0.3$, $P = 0.70$; and PAS MU: $t = -3.7$, $P = 0.007$]. Similar statistical effects were observed in the ADM muscle: effect of time [$F = 89.22$, $P < 0.001$]; time × group interaction [$F = 29.73$, $P < 0.001$]; and

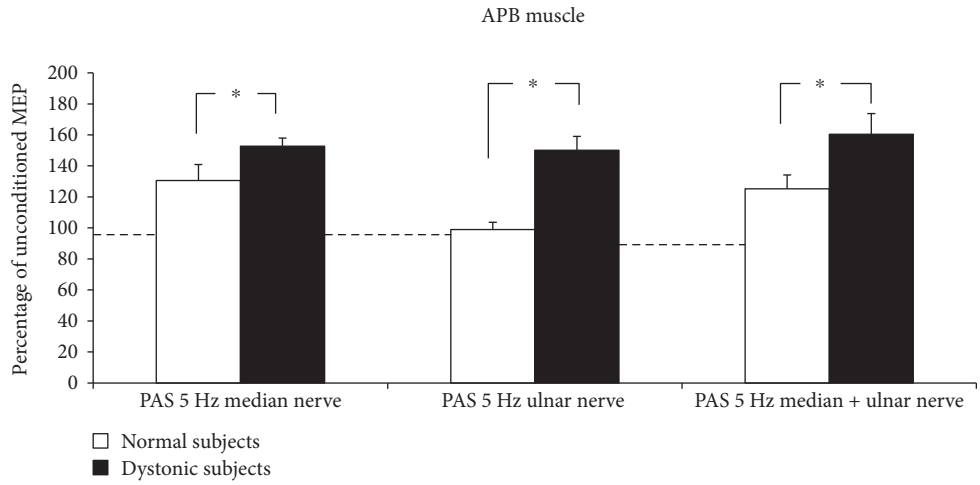


Figure 1: 5 Hz rPAS induced an increase in MEP size recorded from APB muscle in both patients and controls; repeated measure ANOVA showed a significant effect of time [$F = 88.38$; $P < 0.001$], but the amount of facilitation was different between the two groups, as shown by the time × group interaction [$F = 21.14$; $P < 0.001$].

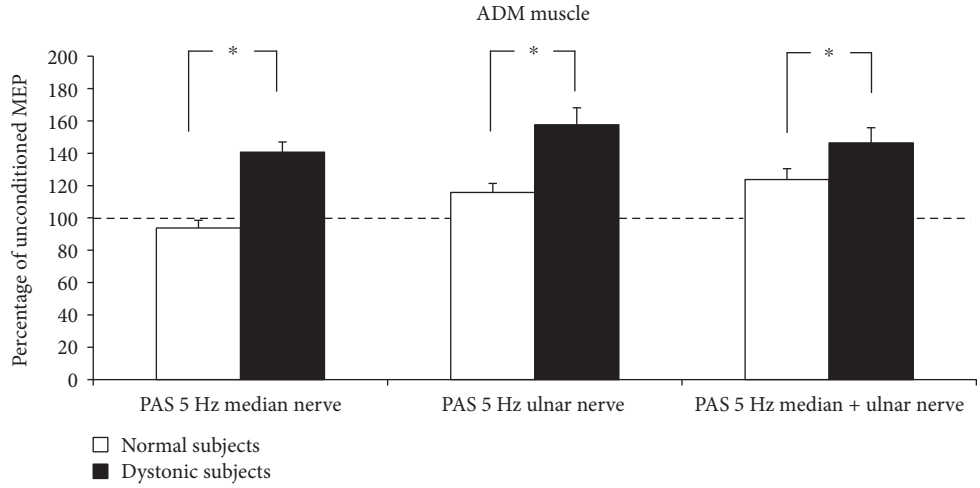


Figure 2: 5 Hz rPAS induced an increase in MEP size recorded from ADM muscle in both patients and controls; repeated measure ANOVA showed a significant effect of time [$F = 89.22$; $P < 0.001$] and time × group interaction [$F = 29.73$; $P < 0.001$].

time × group × conditioning interaction [$F = 1.68$, $P = 0.19$] (Figure 2). Post hoc t-test revealed again that in dystonic patients all the three types of intervention induced a significant increase in MEP facilitation [PAS M: $t = -5.8$, $P = 0.001$; PAS U: $t = -5.7$, $P = 0.001$; and PAS MU: $t = -6.3$, $P < 0.001$], while in controls, only PAS U and PAS MU induced changes in MEP amplitude but not PAS M [PAS M: $t = 1.6$, $P = 0.15$; PAS U: $t = -2.7$, $P = 0.03$; and PAS MU: $t = -4.6$, $P = 0.002$]. Factorial ANOVA did not show any significant difference between the amount of ratio MU/(M + U) ∗ 100 after the 5 Hz rPAS between dystonic patients and controls in the APB muscle. In both groups, indeed, the percentage of inhibition was around 50% [$F = 0.596$; $P = 0.562$] (Figure 3(a)). The same amount of inhibition was found in the ADM muscle for both patients and controls [$F = 3.493$; $P = 0.07$] (Figure 3(b)). In both normal subjects and focal dystonic patients, N20 SEP amplitudes of the S2 response were significantly inhibited at ISIs of 20 and 40 ms with respect to those of the S1 control response; more specifically, SEP amplitudes of the test S2 response were always smaller than those of the control S1 response. The (S2/S1) ∗ 100 ratio of all central SEPs did not differ between patients and controls at the ISI of 20 and 40 ms [ISI 20 ms: $Z = -0.4$, $P = 0.62$; ISI 40 ms: $Z = -0.9$, $P = 0.32$] (Figure 4). Finally, the MU/(M + U) ∗ 100 ratio of the cortical N20 SEP was not significantly different between dystonic patients and controls [$Z = -0.2$; $P = 0.8$] (Figure 5).

4. Discussion

Four main findings clearly emerge from this study:

(1) All type of conditioning protocols (PAS M, PAS U, and PAS MU) can induce long-lasting plastic

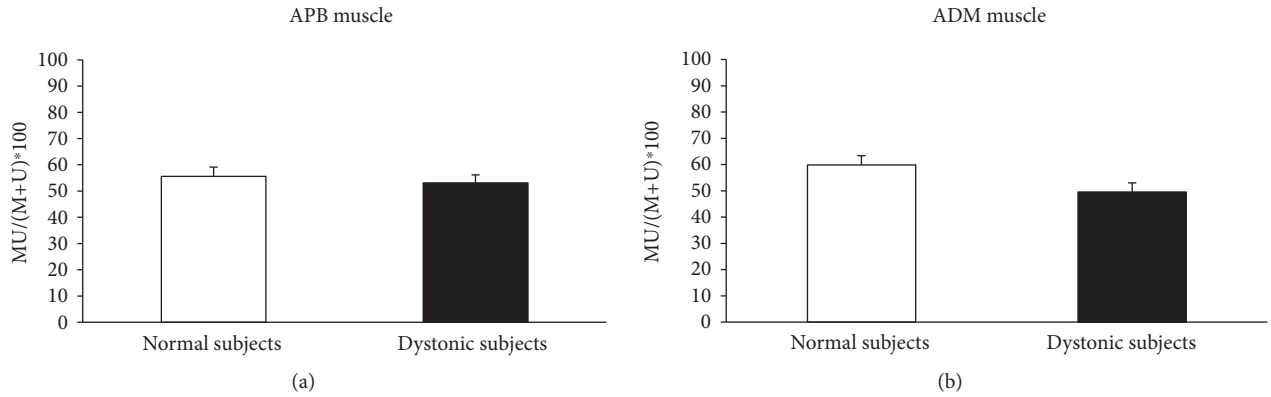


Figure 3: 5 Hz rPAS did not induce any significant difference between the amount of ratio MU/(M + U) ∗ 100 after the 5 Hz rPAS between dystonic patients and controls in the APB and ADM muscles (factorial ANOVA APB: $F = 0.596$, $P = 0.562$ (a); ADM: $F = 3.493$, $P = 0.07$ (b)).

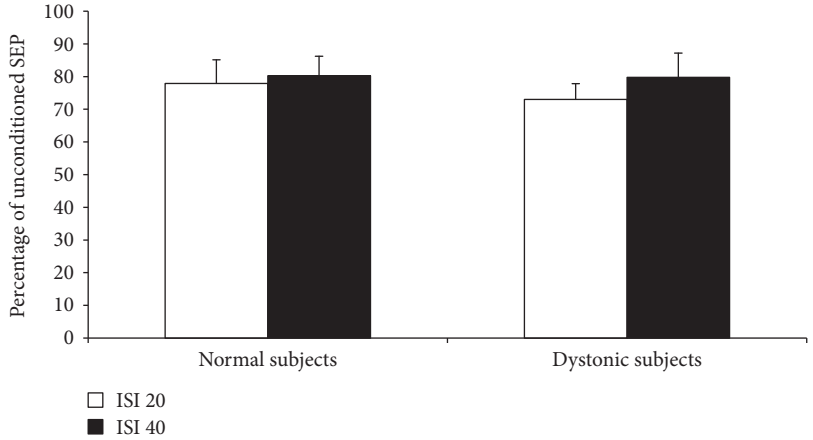


Figure 4: In normal subjects and focal dystonia patients, N20 SEP amplitudes of the S2 response were significantly suppressed at ISIs of 20 and 40 ms with respect to those of the S1 control response. The (S2/S1) ∗ 100 ratio of all central SEPs did not differ between patients and controls at the ISI of 20 and 40 ms (unpaired Mann Whitney U test: ISI 20 ms: $Z = -0.4$, $P = 0.62$; ISI 40 ms: $Z = -0.9$, $P = 0.32$).

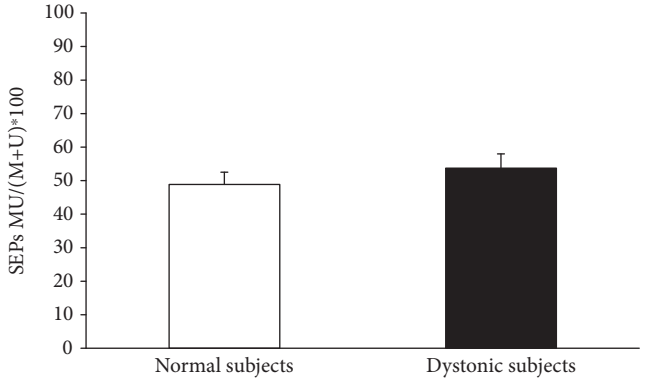


Figure 5: The MU/(M + U) ∗ 100 ratio of the cortical N20 SEP was not significantly different between dystonic patients and controls (unpaired Mann Whitney U test: $Z = -0.2$, $P = 0.8$).

changes in cortical excitability of both dystonic patients and normal subjects

(2) In keeping with previous findings, focal hand dystonia patients had two main abnormalities. First, associative plasticity after PAS25 was enhanced compared to normal subjects; second, the spatial specificity was lost so that facilitation was observed in both median and ulnar innervated muscles

(3) The inhibitory integration of somatosensory inputs as well as the somatosensory inhibition are normal in patients with focal dystonia

(4) Surround inhibition phenomena are normal in focal dystonia when applying PAS-induced sensory-motor plasticity protocol

4.1. PAS Aftereffects. Our results confirm that 5 Hz rPAS at an interstimulus interval of 25 ms can promote lasting changes in cortical excitability. Considering that rPAS aftereffects are long lasting, reversible, and topographically specific [12], this protocol is reminiscent of Hebbian plasticity models described in animal experimentation. A main advantage of rPAS protocol is the short duration of conditioning which makes this technique ideal to apply in patients [15]. In keeping with previous studies, we found a stronger increase in corticospinal excitability after rPAS in dystonic

patients than in healthy controls. In addition, patients with dystonia showed loss of topographical specificity of PAS-induced effects, with facilitation spreading over median and ulnar innervated muscles, while in healthy individuals the increase in excitability only occurred in APB muscle innervated by the median nerve but not in the ADM muscle innervated by the ulnar nerve. The loss of spatial specificity is perhaps the most important and robust finding and could be related to the abnormalities of neuronal inhibition within motor cortex already identified in dystonic patients [16]. It is to point out that this excess of motor cortex plasticity is not confined to the clinically affected regions by dystonia but generalize across the entire sensorimotor system, representing an endophenotypic trait of the disease [17–20]. Although these findings have been reproduced by different groups [21–23], in one study, it has been reported that the effects of PAS were highly variable, and they conclude that enhanced plasticity should not be considered a dystonic fingerprint because the direction of response can vary, and there is an overlap between patient and healthy data [24].

4.2. Lateral Inhibition during PAS and within Somatosensory System. Inhibitory integration of somatosensory inputs as well as the somatosensory inhibition phenomena evaluated in our population of dystonic patients did not show any abnormalities compared with the ones of normal subjects. These findings support the idea that the temporal and spatial integration along somatosensory pathways are normal at least in focal hand dystonia, and this could explain the normal integration of the simultaneous median-ulnar nerve stimulation after PAS. On the other hand, our data confirm again that in focal hand dystonia there is a clear abnormality in sensory-motor plasticity as indexed by the loss of spatial specificity after PAS that may account for the creation of abnormal motor engrams. PAS topographical specificity has a different mechanism since the afferent stimulation is not dual and is probably related to the alteration of inhibitory phenomena within motor cortex which are lost in dystonia. These results can be apparently in contrast with the previous findings of Tinazzi and coworkers and Frasson and coworkers [5, 9]. Indeed, they found an abnormal somatosensory inhibition and sensory integration of afferent proprioceptive inputs. However, in both studies, the majority of patients were affected by generalized or segmental dystonia with only two patients having FHD [5, 9]. On the contrary, in our study, we only included a population affected by FHD. In a recent paper, Antelmi and coworkers [25] found a reduced suppression of SEPs in cervical dystonia at the ISI of 20 and 40 milliseconds, not confirmed in our study and in the study of Tamura and coworkers [26]. These contrasting results could be related to the fact that in the study of Antelmi and coworkers, SEPs were elicited by stimulation of the digital nerves of the index finger rather than the median nerve at the wrist. In the same paper, Antelmi and coworkers found an abnormal sensory integration in spatial domain in cervical dystonia, but again, this contrasting result might be due to the different methodology employed in the two studies [25].

4.3. Data Interpretation. In conclusion, the data of the present study suggest, in contrast with previous ones, that surround inhibition along somatosensory pathways are intact in FHD. In addition, we demonstrated that surround inhibition is also normal during the induction of sensory-motor plasticity phenomena. These results may suggest that, at least in FHD, spatial and temporal processing of sensory inputs are normal in patients with FHD despite the well-known alterations of spatial and temporal tactile discrimination, which are related to dysfunction in somatosensory cortex (S1) [26–29]. In a previous paper, Tamura and coworkers showed in FHD a reduction of inhibition of the P27 SEP component after a double stimulation of the median nerve at 5 ms interval, and they correlated this alteration with the abnormalities of temporal tactile discrimination. Similarly, the authors did not find any reduction of inhibition of N20 and P27 component at 20 and 40 ms intervals, as demonstrated in the present study [26]. On the other hand, Frasson and coworkers found a reduction of inhibition at 20 and 40 ms interval with a normalcy at 5 ms which was not confirmed by Tamura [9]. Therefore, future studies are needed to better clarify the link between the physiological mechanisms in tactile discrimination within S1 and the correlation with the cortical SEP components in healthy subjects and in the different form of dystonia. On the other hand, considering that spatial and temporal processing of sensory inputs are clearly abnormal in patients with generalized dystonia as demonstrated in the study of Tinazzi et al. and Frasson et al. [5, 9], we can speculate that a progressive loss of surround inhibition phenomena may contribute to the spreading and subsequent generalization of dystonia. Therefore, we can hypothesize that the greater is the spreading of dystonia in the body parts, the lesser is the ability to integrate and discriminate afferent sensory inputs coming simultaneously from adjacent body parts which could be subject of a subsequent study.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Consent

Informed consent was obtained from the patients after the nature and possible consequences of the studies were explained.

Conflicts of Interest

Dr. Francesca Morgante has received honoraria as a Consultant & Advisory Boards from Medtronic and Chiesi. She has received honoraria for speaking from UCB Pharma, Medtronic, Lundbeck, Chiesi, and Abbvie. She serves in the Editorial board of Movement Disorders Clinical Practice and Frontiers in Movement Disorders. The other authors do not report any financial disclosure and have no professional or financial affiliations that might be perceived as having biased the presentation.

Authors' Contributions

C. Terranova and V. Rizzo contributed equally to this work. They shared the authorship of this work.

References

[1] M. Hallett, "The neurophysiology of dystonia," *Archives of Neurology*, vol. 55, no. 5, pp. 601–603, 1998.

[2] A. Quartarone, H. R. Siebner, and J. C. Rothwell, "Task-specific hand dystonia: can too much plasticity be bad for you?," *Trends in Neurosciences*, vol. 29, no. 4, pp. 192–199, 2006.

[3] Y. H. Sohn and M. Hallett, "Disturbed surround inhibition in focal hand dystonia," *Annals of Neurology*, vol. 56, no. 4, pp. 595–599, 2004.

[4] J. W. Mink, "The basal ganglia: focused selection and inhibition of competing motor programs," *Progress in Neurobiology*, vol. 50, no. 4, pp. 381–425, 1996.

[5] M. Tinazzi, A. Priori, L. Bertolasi, E. Frasson, F. Mauguière, and A. Fiaschi, "Abnormal central integration of a dual somatosensory input in dystonia: evidence for sensory overflow," *Brain*, vol. 123, no. 1, pp. 42–50, 2000.

[6] G. Abbruzzese, R. Marchese, A. Buccolieri, B. Gasparetto, and C. Trompetto, "Abnormalities of sensorimotor integration in focal dystonia: a transcranial magnetic stimulation study," *Brain*, vol. 124, no. 3, pp. 537–545, 2001.

[7] S. Tamburin, P. Manganotti, C. A. Marzi, A. Fiaschi, and G. Zanette, "Abnormal somatotopic arrangement of sensorimotor interactions in dystonic patients," *Brain*, vol. 125, no. 12, pp. 2719–2730, 2002.

[8] L. Bertolasi, S. Romito, M. Tinazzi, N. Rizzuto, and A. Priori, "Impaired heteronymous somatosensory motor cortical inhibition in dystonia," *Movement Disorders*, vol. 18, no. 11, pp. 1367–1373, 2003.

[9] E. Frasson, A. Priori, L. Bertolasi, F. Mauguière, A. Fiaschi, and M. Tinazzi, "Somatosensory disinhibition in dystonia," *Movement Disorders*, vol. 16, no. 4, pp. 674–682, 2001.

[10] K. Stefan, E. Kunesch, L. G. Cohen, R. Benecke, and J. Classen, "Induction of plasticity in the human motor cortex by paired associative stimulation," *Brain*, vol. 123, no. 3, pp. 572–584, 2000.

[11] A. Quartarone, S. Bagnato, V. Rizzo et al., "Abnormal associative plasticity of the human motor cortex in writer's cramp," *Brain*, vol. 126, no. 12, pp. 2586–2596, 2003.

[12] A. Quartarone, V. Rizzo, S. Bagnato et al., "Rapid-rate paired associative stimulation of the median nerve and motor cortex can produce long-lasting changes in motor cortical excitability in humans," *The Journal of Physiology*, vol. 575, no. 2, pp. 657–670, 2006.

[13] M. P. Sheehy and C. D. Marsden, "Writers' cramp-a focal dystonia," *Brain*, vol. 105, no. 3, pp. 461–480, 1982.

[14] P. M. Rossini, A. T. Barker, A. Berardelli et al., "Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee," *Electroencephalography and Clinical Neurophysiology*, vol. 91, no. 2, pp. 79–92, 1994.

[15] K. Stefan, M. Wycislo, and J. Classen, "Modulation of associative human motor cortical plasticity by attention," *Journal of Neurophysiology*, vol. 92, no. 1, pp. 66–72, 2004.

[16] M. Hallett, "Neurophysiology of dystonia: the role of inhibition," *Neurobiology of Disease*, vol. 42, no. 2, pp. 177–184, 2011.

[17] D. Weise, A. Schramm, M. Beck, K. Reiners, and J. Classen, "Loss of topographic specificity of LTD-like plasticity is a trait marker in focal dystonia," *Neurobiology of Disease*, vol. 42, no. 2, pp. 171–176, 2011.

[18] A. Quartarone and A. Pisani, "Abnormal plasticity in dystonia: disruption of synaptic homeostasis," *Neurobiology of Disease*, vol. 42, no. 2, pp. 162–170, 2011.

[19] A. Quartarone, V. Rizzo, and F. Morgante, "Clinical features of dystonia: a pathophysiological revisitation," *Current Opinion in Neurology*, vol. 21, no. 4, pp. 484–490, 2008.

[20] A. Quartarone, V. Rizzo, C. Terranova et al., "Sensory abnormalities in focal hand dystonia and non-invasive brain stimulation," *Frontiers in Human Neuroscience*, vol. 8, 2014.

[21] D. Belvisi, A. Suppa, L. Marsili et al., "Abnormal experimentally- and behaviorally-induced LTP-like plasticity in focal hand dystonia," *Experimental Neurology*, vol. 240, pp. 64–74, 2013.

[22] S. Meunier, H. Russmann, E. Shamim, J. C. Lamy, and M. Hallett, "Plasticity of cortical inhibition in dystonia is impaired after motor learning and paired-associative stimulation," *The European Journal of Neuroscience*, vol. 35, no. 6, pp. 975–986, 2012.

[23] P. Schwingenschuh, D. Ruge, M. J. Edwards et al., "Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study," *Movement Disorders*, vol. 25, no. 5, pp. 560–569, 2010.

[24] A. Sadnicka, M. Hamada, K. P. Bhatia, J. C. Rothwell, and M. J. Edwards, "A reflection on plasticity research in writing dystonia," *Movement Disorders*, vol. 29, no. 8, pp. 980–987, 2014.

[25] E. Antelmi, R. Erro, L. Rocchi et al., "Neurophysiological correlates of abnormal somatosensory temporal discrimination in dystonia," *Movement Disorders*, vol. 32, no. 1, pp. 141–148, 2016.

[26] Y. Tamura, M. Matsuhashi, P. Lin et al., "Impaired intracortical inhibition in the primary somatosensory cortex in focal hand dystonia," *Movement Disorders*, vol. 23, no. 4, pp. 558–565, 2008.

[27] A. Conte, L. Rocchi, A. Nardella et al., "Theta-burst stimulation-induced plasticity over primary somatosensory cortex changes somatosensory temporal discrimination in healthy humans," *PLoS One*, vol. 7, no. 3, article e32979, 2012.

[28] F. M. Molloy, T. D. Carr, K. E. Zeuner, J. M. Dambrosia, and M. Hallett, "Abnormalities of spatial discrimination in focal and generalized dystonia," *Brain*, vol. 126, no. 10, pp. 2175–2182, 2003.

[29] F. Morgante, M. Tinazzi, G. Squintani et al., "Abnormal tactile temporal discrimination in psychogenic dystonia," *Neurology*, vol. 77, no. 12, pp. 1191–1197, 2011.

Hindawi
Neural Plasticity
Volume 2018, Article ID 6798712, 10 pages
https://doi.org/10.1155/2018/6798712

Review Article

Proteostasis and Mitochondrial Role on Psychiatric and Neurodegenerative Disorders: Current Perspectives

Pablo Olivero,[1,2] **Carlo Lozano**,[1,2,3] **Ramón Sotomayor-Zárate**,[4] **Nicolás Meza-Concha**,[1] **Marcelo Arancibia**,[1] **Claudio Córdova**,[1] **Wilfredo González-Arriagada**,[2,5] **Ricardo Ramírez-Barrantes**,[6] **and Ivanny Marchant**[1,2]

[1]*Laboratorio de Estructura y Función Celular, Escuela de Medicina, Facultad de Medicina, Universidad de Valparaíso, Hontaneda 2664, 2341386 Valparaíso, Chile*
[2]*Centro Interoperativo en Ciencias Odontológicas y Médicas, Universidad de Valparaíso, Valparaíso, Chile*
[3]*Servicio de Anatomía Patológica, Hospital Carlos van Buren, San Ignacio 725, Valparaíso, Chile*
[4]*Laboratorio de Neuroquímica y Neurofarmacología, Centro de Neurobiología y Fisiopatología Integrativa, Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile*
[5]*Patología y Diagnóstico Oral, Facultad de Odontología, Universidad de Valparaíso, Valparaíso, Chile*
[6]*Escuela de Tecnologia Medica, Universidad Andres Bello, Quillota 980, 2531015 Viña del Mar, Chile*

Correspondence should be addressed to Ricardo Ramírez-Barrantes; ricardo.ramirez@unab.cl
and Ivanny Marchant; ivanny.marchant@uv.cl

Received 2 February 2018; Revised 13 April 2018; Accepted 17 May 2018; Published 27 June 2018

Academic Editor: Paola Bonsi

Proteostasis involves processes that are fundamental for neural viability. Thus, protein misfolding and the formation of toxic aggregates at neural level, secondary to dysregulation of the conservative mechanisms of proteostasis, are associated with several neuropsychiatric conditions. It has been observed that impaired mitochondrial function due to a dysregulated proteostasis control system, that is, ubiquitin-proteasome system and chaperones, could also have effects on neurodegenerative disorders. We aimed to critically analyze the available findings regarding the neurobiological implications of proteostasis on the development of neurodegenerative and psychiatric diseases, considering the mitochondrial role. Proteostasis alterations in the prefrontal cortex implicate proteome instability and accumulation of misfolded proteins. Altered mitochondrial dynamics, especially in proteostasis processes, could impede the normal compensatory mechanisms against cell damage. Thereby, altered mitochondrial functions on regulatory modulation of dendritic development, neuroinflammation, and respiratory function may underlie the development of some psychiatric conditions, such as schizophrenia, being influenced by a genetic background. It is expected that with the increasing evidence about proteostasis in neuropsychiatric disorders, new therapeutic alternatives will emerge.

1. Introduction

Ramón y Cajal, a pioneer in neuroscience, was the first to describe neurons as brain units that compose "cellular societies," from the point of view of functional morphology [1]. The story continues at the *Université de Paris*, where doctor Jean-Martin Charcot creates a chair on which all modern neurobiology develops. In fact, the autopsies performed by Charcot in illegitimate prostitutes' sons at the *Hôpital de la Salpêtrière* would change the vision of emerging neurobiology forever. Thanks to his contribution, it was possible to determine the existence of certain neuromuscular diseases and rudimentarily identify pathologies such as multiple sclerosis and Parkinson's disease. One hundred sixty years later, neuropathology could contribute to the study of neurodegenerative disorders through conventional techniques, for example, histopathology, histochemistry, or immunohistochemistry applied to the analysis of changes in normal

distribution of various types of proteins in neurons and tissues. Then, in the 90s, the presence of the so-called inclusion bodies was demonstrated in prevalent neurodegenerative conditions like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis, polyglutamine diseases, and the Lewy body dementia. At the same time, immunohistochemistry revealed the role of the ubiquitin-proteasome system and molecular chaperones in the formation of inclusion bodies, particularly in AD and PD [2–7]. Nowadays, we know that besides neuronal involution and reactive gliosis, most neurodegenerative diseases are characterized by protein accumulation.

In protein biosynthesis, metabolic changes, mutations, and stress are frequent conditions that cause protein misfolding and hamper proper biological function. Being molecular machineries whose constituent elements are chaperones, the ubiquitin-proteasome system and the autophagy-lysosomal system [8, 9] constantly counteract these risks by avoiding the accumulation of nondegradable protein aggregates and the consequent cellular malfunction and death [10]. Preserving proteostasis, that is, stable conditions during processes such as biogenesis, folding, trafficking, or degradation of proteins, is crucial to guaranteeing cell functions and the ability to elaborate pertinent reactions to tissue-specific chronic and acute stressors [11]. Dysregulation of the conservative mechanisms of proteostasis involves processes that are fundamental for the viability of postmitotic cells such as neurons and has been associated with several neurodegenerative diseases, such as AD, PD, and HD, among others [12]. Thereby, with increasing knowledge about changes in the tissue protein distribution, new pathogenic mechanisms could be revealed as potential therapeutic targets, especially in the study of the ubiquitin-proteasome system and molecular chaperones [8, 13]. Besides, it has been observed that impaired mitochondrial function, which is influenced by the ubiquitin-proteasome system and chaperones, may also have effects on neurodegenerative disorders [14]. In the present work, we will review the main findings on the neurobiological implications of proteostasis, from a molecular perspective, in relation to the development of neurodegenerative and neuropsychiatric diseases. We discuss the genetic and molecular considerations of mitochondrial dysfunction, an important organelle in proteostasis, in schizophrenia. We conducted an exhaustive bibliographic search through the available articles on MEDLINE/PubMed database. Here, we present the main findings of the available literature, focusing on three main topics: (1) proteostasis in neurodegenerative disease, (2) TRPV1 and proteostasis, and (3) proteostasis and mitochondrial dysfunction in schizophrenia.

1.1. Proteostasis in Neurodegenerative Disease. The efficiency of the cellular physiological processes depends on proper protein localization and function. There is a molecular network that participates in the intricate mechanisms of synthesis, folding, trafficking, and degradation necessary to ensure the structure and function of proteins [15]. The maintenance of proteostasis thus involves the translational and folding machinery including their regulatory systems such as the unfolded protein response (UPR), as well as the large group of molecular chaperones such as HSP70, HSP90, DNAJ/HSP40, chaperonin/HSP60, and small HSP (sHSP) families [16, 17], which balance protein function and turnover. Chaperones' ATP-dependent function is impaired in cellular stress condition. Thus, poor physical recognition by chaperone networks and cellular metabolic stress condition may contribute to protein aggregation in aging and disease [18]. Proteins can be degraded individually or massively mainly in proteasomes by the ubiquitin-proteasome system (UPS) [15]. The UPS is part of the extensive system for protein quality control of neurons and other types of cells, regulating the degradation of misfolding or aberrant proteins to prevent detrimental aggregation. The proteins that will be degraded by the UPS are first ubiquitylated via a series of enzymatic reactions involving ubiquitin-activating (E1), conjugation (E2), and ligase (E3) enzymes [15]. Proteasomes include two subcomplexes, the core particle (CP, 20S) which is a barrel-shaped structure composed of four stacked rings, two identical outer α rings and two identical inner β rings, which carry the catalytic activity, and the regulatory particle (19S) which caps the extremities of the barrel and regulates the entry of ubiquitylated proteins into the catalytic center. The proteasomal network composition is highly dynamic; the levels of molecular chaperones and proteasome subunits can increase or decrease globally or specifically in some compartment, depending on factors such as environmental changes, genetic factors, and aging phenomena [19]. These changes lessen the ability of cells to regulate the accumulation of misfolded proteins, which can induce cell dysfunction and death [15]. The UPS in particular is able to modulate synaptic physiology both pre- and postsynaptically. UPS participation in the neuronal synapse implies regulating calcium channels and may have an impact on long-term memory [20].

Dysfunction of the proteostatic network decreases neuronal plasticity [21–23]. It has been reported that in response to LTP-inducing stimuli in the hippocampus, the activity of the proteasomes increases and also after activation of NMDAR [19]. The kinase CaMKIIα is activated by an entry of calcium via NMDAR which in turn phosphorylates and enhances the proteolytic activity of the proteasome, coupling the synaptic excitation with changes in proteostasis [19].

In mammalian neurons, proteasomal complexes attached to the plasma membrane have been described as nonconventional protein secretion systems. Once the proteins are degraded by these kinds of proteasomes, they are released into the extracellular space which in turn can stimulate postsynaptic neurons via NMDA-type receptors (involved in memory and learning). In addition, they are able to activate signals mediated by calcium [21]. Also, the application of proteasome inhibitors like MG132 induces a fast and several-fold increase in the frequency of spontaneous postsynaptic currents at excitatory and inhibitory synapses, which is independent of the accumulation of ubiquitylated proteins and specific by modulation of presynaptic neurons increasing the neurotransmitter release [24]. Furthermore, the inhibition of the proteasome system induces cell death in several cell types [22]. In neurons, the inhibition of proteasome has been shown to diminish the increase of cytosolic calcium that precedes programmed cell death, for example,

before the activation of caspase-3 [22]. The progress of programmed cell death is very complex and depends on an orchestrated activation of proteins where calcium plays an important role. Experiments in primary cultures of neurons show that the activation of either a voltage-gated calcium channel or exchanger Na^{+}-Ca^{2+} in the plasma membrane during the initial steps in cell death attenuates the damage via increase of cytosolic Ca^{2+}. The inhibition of proteasome blocks this mechanism by reducing the increase of cytosolic calcium mediated by voltage-gated calcium channels [22]. Proteasome is also involved in other neural plasticity events like axonal growth, axonal guidance, and dendritic branching [23]. Failure of the proteostasis network may thus impede directly or indirectly the plasticity of neurons, by favoring the accumulation of aberrant proteins or modulating excitability, synapses, and growth.

Neurodegenerative diseases, which involve degradation of axons, loss of synapses, impairment of synaptic plasticity, and death of neurons, are one of the most enigmatic problems in medicine. Knowledge regarding these diseases has evolved from phenomenology description to mechanistic analysis, the hallmark being the aggregation and deposition of misfolded proteins [19]. AD, PD, and HD are today characterized by disrupted proteostasis, due to decreased function of the UPS, the accumulation of ubiquitylated proteins, and their aggregation, causing progressive neuronal dysfunction and death. Although ubiquitylated proteins can be localized in different brain areas, their high accumulation seems to be a common mechanism in all the diseases abovementioned and the UPS has been involved as primary or secondary cause. Mutations in genes encoding for UPS proteins [25] have also been associated with the development of hereditary forms of neurodegenerative diseases. Recent evidence shows that Aβ peptides, α-synuclein, and mutant huntingtin protein, which are at the origin of the three most important neurodegenerative diseases, share a specific oligomeric conformation that impairs proteasome function. According to this study, the shared three-dimensional structure allows these oligomers to potently inhibit 20S and 26S proteasome gate opening, thus drastically reducing its function. This effect blocks the degradation of proteins favoring its abnormal accumulation [26]. In neurodegenerative disease, as previously described in prion diseases [27], the misfolding protein acts as a template and interacts directly with the native protein and converts the latter into a misfolded replicate. This is the process that aberrant proteins use to recruit and propagate intracellularly the misfolding protein [28]. This seeded aggregation mechanism is employed by Aβ peptide, α-synuclein, and tau protein [28]. The accumulation of these proteins impairs the normal neuronal functions by altering the synaptic transmission [29] and causing cell death.

Besides neuronal dysfunction due to the accumulation of proteins, neurodegenerative disease could change the total protein expression. In particular in AD, a novel approach investigating postmortem the frontal cortex of sporadic AD patients using an integrated method of mass spectrometry-based quantitative proteomics revealed several clusters of modification of protein expression [30]. Using this method, the authors found 487 differentially expressed proteins with significantly altered levels. From this pool of proteins, 262 were upregulated while 225 were downregulated. In general terms, several functions in AD are altered which include proteostasis, RNA homeostasis, immune response, neuroinflammation, synaptic transmission, vesicular transport, cell signaling, cellular metabolism, lipid homeostasis, mitochondrial dynamics and function, cytoskeleton organization, and myelin-axon interactions. The identification of a wide spectrum of protein alterations strengthens the multifactorial and complex etiology of neurodegenerative disease and how the accumulation of altered proteins could alter completely the homeostasis of protein expression [30]. In the same line, AD proteomic applications indicate that the progression of the disease worsens several processes as energy production, signal transduction, synaptic plasticity, proteasome function, cellular morphology, and cell cycle [31].

In addition to protein misfolding and impaired proteostasis, neurodegenerative diseases are linked to imbalance of mitochondrial fission and fusion associated with an increase in oxidative stress. The association of mutant aberrant proteins with mitochondrial membrane has been reported to cause mitochondrial fragmentation, leading to mitochondrial dysfunction with concomitant production and liberation of reactive oxygen species. It is believed that this response would promote mitochondrial clearance by the cellular autophagic machinery via a process termed mitophagy [32], although the excess of activation of mitophagy could contribute to long-term neuronal degeneration [32]. This phenomenon is illustrated by PD where the abnormally degraded ubiquitylated proteins and α-synuclein often bind to mitochondrial membrane inducing mitochondrial dysfunction [33, 34].

Proteostasis is not limited to the cytoplasm only; it may occur in other cellular compartments. The most prominent are mitochondria and endoplasmic reticulum (ER), both organelles sharing multiple functions as calcium storage and lipid metabolism [35]. ER is considered the major site of cellular protein synthesis. One-third of the human proteome is synthesized in the ER, consisting in secreted proteins, integral membrane proteins, and functional proteins that connect the activity of ER and other organelles such as mitochondria [36].

C. elegans, *Drosophila*, and mammals, for instance, exhibit a mitochondrial unfolded protein response (mtUPR) against proteotoxic stress. This response could be activated by a wide range of noxious stimuli like depletion of mtDNA, impairment of mitochondrial chaperones or proteases, high concentration of ROS, or expression of misfolded proteins [37]. In general terms, this reaction consists in upregulating target genes that include organelle-specific chaperones and proteases to avoid the accumulation of toxic proteins [37]. Notably, this stress response is conserved in a cell culture model of HD, suggesting a general mechanism against stress [37].

Additional mechanisms may contribute to coordinated protein degradation between mitochondria and cytoplasm. The proteasome has been implied in the extraction and degradation of misfolded proteins of the mitochondrial outer membrane [38, 39]. In addition, it is possible that aggregates

of cytosolic proteins can be sent to the mitochondria for their degradation by mitochondrial proteases [40]. Although this phenomenon remains incompletely understood, it is possible that the degradation system integrates the different cellular compartments to avoid protein aggregation not only in the cytoplasm but also in vital organelles such as endoplasmic reticulum and mitochondria, which can be altered by the aging process and neurodegenerative diseases. We present here below some examples of proteins involved in prevalent diseases and their particular role in neuron degeneration.

1.1.1. Tau Protein. Tau protein is abundant in the central nervous system, and its main physiological function is to stabilize the cytoskeleton through binding to microtubules [41, 42]. Recent information indicates that tau protein is involved in several other processes such as synaptic plasticity and memory. A knockout mouse model for tau ($Mapt^{-/-}$) evidenced aging-dependent short-term memory deficits, synaptic plasticity flaws, and impairment in long-term potentiation [43]. Some posttranslational modifications in tau protein such as phosphorylation, glycosylation, and ubiquitylation have been associated with neuropathologies. At the cellular level, Pick disease—a frontotemporal dementia that initiates with personality changes—is characterized by a large aggregation of hyperphosphorylated tau proteins that leads to production of Pick bodies [44, 45]. On the other hand, gliofibrillary tangles that characterize AD are composed of hyperphosphorylated tau proteins confined mainly to the entorhinal cortex [46, 47]. The accumulation of hyperphosphorylated tau is due to defective proteasomal degradation that may contribute to the build-up of tangles. In addition to phosphorylation, tau is also acetylated, and this modification impairs the proteasomal degradation and enhances the accumulation of tau. Together with Aβ-peptides, tau declines cognitive function, memory, and synaptic plasticity. These adverse effects produced by the combination of tau and Aβ can be prevented through the ablation of tau expression, leading to the hypothesis that tau is required for Aβ-induced synaptic dysfunction and memory deficits [43].

1.1.2. β-Amyloid. β-Amyloid is also involved in AD. This protein is formed from amyloid precursor protein, which is processed by α-, β-, and γ-secretase [48]. While the form $A\beta_{40}$ is the most common and soluble one, the more hydrophobic form $A\beta_{42}$ is considered the most amyloidogenic and, therefore, predominant component of senile plaques [49]. In fact, a great accumulation of senile plaques is associated with UPS dysfunction with consequent synaptic dysfunction and neuronal loss in cortical and subcortical regions, leading to cognitive impairment, memory loss, and motor disturbances [49].

1.1.3. α-Synuclein and PARK2. α-Synuclein is a soluble protein of 140 amino acids, which is abundant in neurons, and especially concentrated in presynaptic terminals [50]. This chaperone protein plays an important role in mediating protein-protein and protein-lipid interactions [51]. A mutated form of α-synuclein in patients with PD has been described [52], and again, the UPS is the main perturbed system favoring the accumulation of this protein. Selective inactivation of 26S proteasomes in substantia nigra dopaminergic neurons in a conditional knockout mouse model results in neurodegeneration and ubiquitin-positive aggregates resembling Lewy bodies (accumulation of α-synuclein). At a cognitive level, α-synuclein overexpression would induce a progressive loss of emotional memory secondary to mesolimbic dopaminergic dysfunction [53].

Parkin protein, now known as parkin RBR E3 ubiquitin-protein ligase (PARK2) [54], is part of the complex E3 ubiquitin ligase, necessary for the action of the ubiquitin-proteasome system. Parkin mutations have been associated with a familial form of early-onset PD [55, 56]. Interestingly, patients with PD with parkin mutations lack Lewy bodies, suggesting that parkin may be required for the formation and ubiquitination of these protein aggregates. Parkin has a role in neuroprotection by activating the PI3K-Akt pathway and also by cleansing dysfunctional mitochondria. Without the quality control of parkin, an increase in the number of dysfunctional mitochondria would lead to cell death. The dual-role context dependence of parkin should be better studied to understand neuronal physiology.

1.2. Coordinated Mitochondrial-Endoplasmic Reticulum Function Decline May Be Rescued by TRPV1 Control. The etiology of cognitive decline that occurs with aging is poorly understood; however, it is known that mitochondria are involved in this phenomenon [57]. Altered mitochondrial proteostasis and unfolded protein response could impede mitochondrial fusion and fission processes that normally reduce cell damage [14]. Disruptions of protein folding have also been associated to neurodegenerative disease with accumulation of misfolded proteins in the ER lumen, causing ER stress [35]. Several reports of increase in hyperphosphorylated tau protein in conjunction with stress markers in the ER in postmortem brain samples support this idea [58]. The "calcium hypothesis of brain aging and AD" intends to explain these findings. According to this hypothesis, Aβ would induce the ER to leach calcium that would be consequently taken by the mitochondria [59]. The calcium buffering mediated by mitochondria would induce overload of the ion in the mitochondrial matrix, reactive oxygen species production, and eventually, activation of programs of neuronal death [60, 61].

It should be noted that mammalian aging reduces pain perception associated with tissue damage by targeting the evolutionary conserved transient receptor potential cation channel subfamily V member 1 (TRPV1) that deploys a still unclear molecular mechanism for mitochondrial rescue [62]. TRPV1 mutations delay onset of age-related cognitive decline, maybe through SIRT1-dependent metabolic adaptation, which improves mitochondrial function and enhances several cellular antioxidant mechanisms [63]. The SIRT1 longevity factor is a deacetylase that plays a cytoprotective role in cellular response to stress. It is known that SIRT1 can modulate the heat shock response by deacetylation of the transcription factor HSF1, which triggers the production of molecular chaperones, promoting proteostasis and cellular viability [64]. In that sense, targeting mitochondrial

proteostatic mechanisms, the natural TRPV1 agonist and antioxidant combined treatment synergistically would decrease glutamate toxicity, reactive oxygen species generation, and apoptotic neuronal death, offering a promising therapeutic approach to neurodegenerative disorders [65]. Activation of TRPV1 by capsaicin restores SIRT1 and suppresses NF-κB signaling recovering tissue damage generated by plaques of atheroma [66]. In addition, leptin is able to reduce brain infarct volume and improve functional outcome after stroke via increased expression of TRPV1 and SIRT-1, restoring mitochondrial function and avoiding apoptosis [67].

1.3. Targeting Mitochondrial Dysfunction in Neuropsychiatric Disorders: The Case of Schizophrenia. As stated above, mitochondria have a prominent role in proteostasis [14, 68]. Mitochondria by themselves are responsible for producing cellular energy through the oxidative phosphorylation system, managing calcium buffering, generating reactive oxygen species, and storing regulators related to apoptosis. These functions are physiologically relevant due to the energetically expensive neuronal activities that lead to successful synaptic plasticity or cell death [69]. Many findings point out that mitochondrial function abnormalities are essential components of the underlying neurobiology of a number of neuropsychiatric conditions, including schizophrenia.

1.4. The Role of DISC1. Disrupted in schizophrenia 1 (DISC1) is a scaffold protein involved in the regulation of neuronal proliferation, differentiation, migration, and cytoskeletal modulation [70] which has been extensively linked to schizophrenia and other major mental illnesses [71–73]. Although it is expressed most highly during fetal neurogenesis and in the adult hippocampus, DISC1 is expressed in different brain regions [74] and in other tissues as well [75]. DISC1 interactions with proteins of the dopaminergic system, such as fasciculation and elongation protein zeta 1, phosphodiesterase 4D9 and phosphodiesterase 4B, serine/threonine protein kinase Akt, and glycogen synthase kinase-3, have been studied due to their therapeutic potential [76, 77].

Unregulated expression of DISC1 and aberrant multimerization of DISC1-producing insoluble aggregates that are dysfunctional are associated with chronic neuropsychiatric diseases [75, 77]. Insoluble oligomers of DISC1 have indeed been found in postmortem brain samples of patients with schizophrenia [78]. The DISC1 mutant gene resulting from balanced translocation t(1;11)(q42;q14.3) was first identified in a Scottish lineage, and then it was found in other families, all of them with a history of schizophrenia among other mental disorders [79, 80]. In a recent systematic review, it was concluded that DISC1 would have a role in the regulation of dopaminergic function, installing dopaminergic dysregulation as a possible explanation for the higher rate of schizophrenia observed in patients with the DISC1 variant [77].

Inheritance of maternal mitochondrial DNA variants might be associated with the high prevalence of the disorder in relatives of schizophrenic patients [81]. Thus, Rollins et al. [82] verified that the synonymous base pair substitutions in the coding regions of the mitochondrial DNA genome in the dorsolateral prefrontal cortex of schizophrenics were increased by 22% compared to controls. Mostly found in mitochondria [83], DISC1 has been demonstrated to participate in neurite outgrowth, neurogenesis, neuronal migration, intracellular cAMP signaling, and many other neuronal processes [69]. Mitochondrial overexpressed truncated DISC1 isoforms may determine abnormal mitochondrial morphology, and depletion of DISC1 causes deficiencies in important mitochondrial enzyme activities and interferes mitochondrial trafficking throughout the axons [84]. Hence, the processes mediated by DISC1 in mitochondrial dynamics are necessary for neural development and dendritic branching [85]. Recent findings have shown that DISC1 plays a central role in mitochondrial function in association to mitofilin, a single-span mitochondrial inner membrane protein that is crucial for regulating mitochondrial cristae morphology and for preservation of mitochondrial DNA [69, 86]. DISC1 deficiencies are also linked with mitochondrial dysfunction such as decreased NADH dehydrogenase activity in the electron transport chain, reduced ATP contents, impaired mitochondrial calcium dynamics, and diminished activity of monoamine oxidase, which can be related to the loss of mitofilin stability as well as mitochondrial morphological abnormalities. Particularly, downregulation of monoamine oxidase activity is of utmost interest due to its link with the mesolimbic hyperdopaminergic tone, probably responsible for positive psychotic symptoms. Consequently, monoamine oxidase activity in DISC1-deficient neurons might indeed be a key element in hyperdopaminergic theory [69, 86].

In a critical and recent study of Park et al. [87], DISC1 deficiency is shown to elicit a hyperactivation in endoplasmic reticulum-mitochondrial Ca^{2+} transfer—through the mitochondrial associated endoplasmic reticulum membrane—triggered by oxidative stress and excessive glucocorticoids, causing abnormal mitochondrial Ca^{2+} storage. This process finally triggers an overproduction of ROS mediated by a disruption in mitochondrial membrane potential [87]. The authors concluded that DISC1 modulates neuronal stress response through ER-mitochondrial Ca^{2+} transfer. Thus, DISC1 association with cognitive and emotional deficits implies dysregulation of Ca^{2+} flux between ER and mitochondria through mitochondrion-associated membrane proteins and the consequent loss of proteostasis as a common mechanism shared by aging, as well as neurodegenerative and psychiatric diseases.

In other animal model explorations, DISC1 has been implicated in hypothalamic-pituitary-adrenal dysregulations [88, 89]. Specifically, in a mouse model it has been demonstrated that environmental stressors combined with an appropriate genetic risk can trigger, for example, neurochemical projections originating from the ventral tegmental area and behavioral changes induced by DISC1 expression [89]. Interestingly, these findings have allowed formulating the hypothesis that environmental stressors during childhood and adolescence could exert epigenetic control over the dopaminergic pathways and, therefore, set mental illnesses as schizophrenia.

1.4.1. Dendritic Spines and Mitochondrial Hypoplasia. Different studies indicate that the mitochondrial network displays

important transcriptome alterations in layer III pyramidal cells in schizophrenics, supporting a molecular link between mitochondrial dysfunction and the important decrease in dendritic spine density observed in these neurons [90]. Mitochondria regulate dendritic spine morphogenesis and plasticity but are also involved in the negative regulation of dendritic branching during development. Overall, evidence intrinsically links mitochondrial copy number, localization, and function with dendritic spine morphology and synaptic transmission [91]. In this context, the most frequently found protein in postsynaptic density is PSD-95, a scaffolding protein which belongs to the kinase family. It is implied in excitatory synapses and plays a key role in synaptic plasticity through dendritic spine morphogenesis and long-term potentiation and long-term depression. Postmortem studies carried out in brains of schizophrenic patients have demonstrated a significant decrease in PSD-95 mRNA levels in specific areas as dorsolateral and dorsomedial prefrontal cortices [92]. This may be related to anomalous spine dynamics observed in neurodevelopmental and neuropsychiatric disorders, for example, schizophrenia and autism spectrum disorders [93]. Different explorations in patients with schizophrenia have found decreased numbers of mitochondria in presynaptic buttons in dopaminergic neurons of the substantia nigra [94]. Moreover, a reduction in the number of mitochondria in axons of drug-naïve schizophrenics has also been verified, but not in patients using antipsychotic drugs [95]. Findings also exhibit significant decreases in the mitochondrial density of oligodendroglial cells in the caudate nucleus and prefrontal areas in patients, particularly those with prominent negative symptoms [96].

1.4.2. Inflammation. Neuroprogression, a stage-related phenomenon of neurodegeneration and decline in neuronal plasticity and neurogenesis that has been employed as a research paradigm in schizophrenia, has demonstrated to be significantly influenced by neuroinflammation due to a synergistic effect with mitochondrial dysfunction and neuroprogressive immunoinflammatory, oxidative, and nitrosative stress pathways, activating a vicious cycle that conduces to neuronal death [97, 98]. Novel therapeutic strategies could focus on improving mitochondrial function, through promoting an endogenous antioxidant defense system and antioxidant treatment to compensate mitochondrial injury and increase the mitochondrial respiration rate [97].

Another potential therapeutic target regarding mitochondrial functioning is the translocator protein, located in the outer mitochondrial membrane of steroid-synthesizing nervous cells. It is involved in the permeability to water and small substances at the junction of the inner and outer membranes. Since it is linked with apoptosis and upregulated in some neurodegenerative diseases, this protein has been proposed as an inflammation biomarker and is currently being appraised in clinical trials of drug use [99].

1.4.3. Electron Transport Chain. Diverse neuroimaging studies have demonstrated an altered metabolism expressed as changes in ATP in different brain regions of schizophrenic patients [5]. The severity of negative symptoms and the neuropsychological performance would be correlated with ATP levels [100]. These results point out a dysfunction of brain mitochondrial oxidative phosphorylation, related intrinsically with processes as pre- and postsynaptic action potentials, neurotransmitter release, and postsynaptic currents [101, 102]. Specifically, the expression of multiple complex I subunits of the electron transport chain, such as NDUFV1, NDUFV2, and NDUFS1, is significantly altered in the prefrontal cortex, striatum, hippocampus, and parietooccipital cortex of schizophrenics [102, 103]. In fact, the NDUFV2 gene has been included as a high-risk gene for schizophrenia [104]. In this regard, a study conducted by Robicsek et al. [105] corroborated the impairments in maturation and differentiation into dopaminergic and glutamatergic neurons of schizophrenic-derived pluripotent stem cells, alongside a reduction in complex I-driven respiration, dissipation in mitochondrial membrane potential, altered mitochondrial network structure and connectivity, and aberrant expression degrees of NDUFV1, NDUFV2, and NDUFS1. Some interactions have also been proposed between oxidative phosphorylation and intramitochondrial calcium as complex I, complex II, and complex IV alterations are linked with abnormalities in calcium signaling [106].

With regards to pharmacotherapy, self-defeating findings indicate that typical and atypical antipsychotic drugs would inhibit complex I activity and complex I-driven respiration in isolated mitochondria and in intact neurons [102]. Comparable to these effects, dopamine also affects mitochondrial activity in neuronal cultures by diminishing complex I function and ATP synthesis. These findings could be related to the mitochondrial dopamine uptake, provoking a dose-dependent inhibition of complex I functioning [107]. Both antipsychotics and dopamine inhibit complex I activity, although they interact with the complex at different sites: dopamine interacts with the hydrophilic matrix-penetrating arm and antipsychotics with the hydrophobic inner membrane-embedded arm of the complex. While therapeutic effects of these drugs are due to their antagonism of the D2 receptor, side effects of antipsychotics might be explained by this drug-mitochondria interaction. Besides, dopamine and antipsychotic drugs may interact independently with mitochondria, participating in a compensatory phenomenon with the aim of overcoming mitochondrial dysfunction [102].

2. Conclusions

Our results show that a dysfunction of the proteostasis system is implicated in the etiology of a series of highly prevalent psychiatric and neurodegenerative processes such as PD, dementia, and schizophrenia, among others [12]. Indeed, proteostasis alterations in the prefrontal cortex implicate proteome instability and accumulation of misfolded proteins [45, 47, 49, 76] that could lead to detrimental behavioral and emotional functions in neuropsychiatric disorders [108]. Furthermore, altered mitochondrial dynamics, proteostasis, and mitochondrial unfolded protein response could impede mitochondrial fusion and fission, processes that normally reduce cell damage [14]. This may be related to the decline

in prefrontal cortex performances observed during aging [109]. Mitochondrial alterations, specifically on its genetic bases [69, 86, 110], regulatory role in dendritic development [90, 91] and neuroinflammation [97, 98], could be the underlying phenomena of psychiatric disorders as schizophrenia. In the context of the neuronal relevance of mitochondrial functions [69], we hypothesize that it is possible to delay onset of age-related cognitive decline through metabolic SIRT1-dependent adaptation and improvement of mitochondrial function mediated by TRPV1 control. Thereby, TRPV1 modulation of the mitochondrial proteostasis mechanism could be used to design drug strategies against neural-dependent conditions, such as detrimental cognitive performance. Finally, we expect that with the increasing evidence about proteostasis in psychiatric and neurodegenerative disorders, new therapeutic alternatives will emerge.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to thank Alvaro Cavieres for his precious comments on clinical concepts about neuropsychiatric disease development. This collaborative work was supported by *Fondo Nacional de Desarrollo Científico y Tecnológico*: Fondecyt 11100047 and Fondecyt 11110399.

References

[1] R. R. Llinás, "The contribution of Santiago Ramón y Cajal to functional neuroscience," *Nature Reviews Neuroscience*, vol. 4, no. 1, pp. 77–80, 2003.

[2] E. M. Hol, F. W. van Leeuwen, and D. F. Fischer, "The proteasome in Alzheimer's disease and Parkinson's disease: lessons from ubiquitin B^{+1}," *Trends in Molecular Medicine*, vol. 11, no. 11, pp. 488–495, 2005.

[3] C. P. Dohm, P. Kermer, and M. Bähr, "Aggregopathy in neurodegenerative diseases: mechanisms and therapeutic implication," *Neurodegenerative Diseases*, vol. 5, no. 6, pp. 321–338, 2008.

[4] A. B. Meriin and M. Y. Sherman, "Role of molecular chaperones in neurodegenerative disorders," *International Journal of Hyperthermia*, vol. 21, no. 5, pp. 403–419, 2005.

[5] F. Du, A. J. Cooper, T. Thida et al., "In vivo evidence for cerebral bioenergetic abnormalities in schizophrenia measured using 31P magnetization transfer spectroscopy," *JAMA Psychiatry*, vol. 71, no. 1, pp. 19–27, 2014.

[6] X. Gao and H. Hu, "Quality control of the proteins associated with neurodegenerative diseases," *Acta Biochimica et Biophysica Sinica*, vol. 40, no. 7, pp. 612–618, 2008.

[7] G. Luo and W. Le, "Collective roles of molecular chaperones in protein degradation pathways associated with neurodegenerative diseases," *Current Pharmaceutical Biotechnology*, vol. 11, no. 2, pp. 180–187, 2010.

[8] K. Gadhave, N. Bolshette, A. Ahire et al., "The ubiquitin proteasomal system: a potential target for the management of Alzheimer's disease," *Journal of Cellular and Molecular Medicine*, vol. 20, no. 7, pp. 1392–1407, 2016.

[9] Q. Zheng, T. Huang, L. Zhang et al., "Dysregulation of ubiquitin-proteasome system in neurodegenerative diseases," *Frontiers in Aging Neuroscience*, vol. 8, p. 303, 2016.

[10] M. Press, T. Jung, J. König, T. Grune, and A. Höhn, "Protein aggregates and proteostasis in aging: amylin and β-cell function," *Mechanisms of Ageing and Development*, 2018.

[11] J. A. Reisz, A. S. Barrett, T. Nemkov, K. C. Hansen, and A. D'Alessandro, "When nature's robots go rogue: exploring protein homeostasis dysfunction and the implications for understanding human aging disease pathologies," *Expert Review of Proteomics*, vol. 15, no. 4, pp. 293–309, 2018.

[12] C. Bobori, G. Theocharopoulou, and P. Vlamos, "Molecular chaperones in neurodegenerative diseases: a short review," *Advances in Experimental Medicine and Biology*, vol. 987, pp. 219–231, 2017.

[13] E. L. Friesen, M. L. De Snoo, L. Rajendran, L. V. Kalia, and S. K. Kalia, "Chaperone-based therapies for disease modification in Parkinson's disease," *Parkinson's Disease*, vol. 2017, Article ID 5015307, 11 pages, 2017.

[14] M. J. Baker, T. Tatsuta, and T. Langer, "Quality control of mitochondrial proteostasis," *Cold Spring Harbor Perspectives in Biology*, vol. 3, no. 7, 2011.

[15] J. Labbadia and R. I. Morimoto, "The biology of proteostasis in aging and disease," *Annual Review of Biochemistry*, vol. 84, no. 1, pp. 435–464, 2015.

[16] M. Haslbeck, T. Franzmann, D. Weinfurtner, and J. Buchner, "Some like it hot: the structure and function of small heat-shock proteins," *Nature Structural & Molecular Biology*, vol. 12, no. 10, pp. 842–846, 2005.

[17] Y. E. Kim, M. S. Hipp, A. Bracher, M. Hayer-Hartl, and F. Ulrich Hartl, "Molecular chaperone functions in protein folding and proteostasis," *Annual Review of Biochemistry*, vol. 82, no. 1, pp. 323–355, 2013.

[18] S.-A. Mok, C. Condello, R. Freilich et al., "Mapping interactions with the chaperone network reveals factors that protect against tau aggregation," *Nature Structural & Molecular Biology*, vol. 25, no. 5, pp. 384–393, 2018.

[19] B. Bingol and M. Sheng, "Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease," *Neuron*, vol. 69, no. 1, pp. 22–32, 2011.

[20] T. J. Jarome and F. J. Helmstetter, "The ubiquitin–proteasome system as a critical regulator of synaptic plasticity and long-term memory formation," *Neurobiology of Learning and Memory*, vol. 105, pp. 107–116, 2013.

[21] K. V. Ramachandran and S. S. Margolis, "A mammalian nervous-system-specific plasma membrane proteasome complex that modulates neuronal function," *Nature Structural & Molecular Biology*, vol. 24, no. 4, pp. 419–430, 2017.

[22] S. Wu, K. L. Hyrc, K. L. Moulder, Y. Lin, T. Warmke, and B. J. Snider, "Cellular calcium deficiency plays a role in neuronal death caused by proteasome inhibitors," *Journal of Neurochemistry*, vol. 109, no. 5, pp. 1225–1236, 2009.

[23] A. M. Hamilton and K. Zito, "Breaking it down: the ubiquitin proteasome system in neuronal morphogenesis," *Neural Plasticity*, vol. 2013, Article ID 196848, 10 pages, 2013.

[24] G. V. Rinetti and F. E. Schweizer, "Ubiquitination acutely regulates presynaptic neurotransmitter release in mammalian neurons," *The Journal of Neuroscience*, vol. 30, no. 9, pp. 3157–3166, 2010.

[25] H.-C. Tai and E. M. Schuman, "Ubiquitin, the proteasome and protein degradation in neuronal function and dysfunction," *Nature Reviews Neuroscience*, vol. 9, no. 11, pp. 826–838, 2008.

[26] T. A. Thibaudeau, R. T. Anderson, and D. M. Smith, "A common mechanism of proteasome impairment by neurodegenerative disease-associated oligomers," *Nature Communications*, vol. 9, no. 1, p. 1097, 2018.

[27] J. Rasmussen, M. Jucker, and L. C. Walker, "Aβ seeds and prions: how close the fit?," *Prion*, vol. 11, no. 4, pp. 215–225, 2017.

[28] J. Brettschneider, K. D. Tredici, V. M. Y. Lee, and J. Q. Trojanowski, "Spreading of pathology in neurodegenerative diseases: a focus on human studies," *Nature Reviews Neuroscience*, vol. 16, no. 2, pp. 109–120, 2015.

[29] E. A. André, P. A. Forcelli, and D. T. S. Pak, "What goes up must come down: homeostatic synaptic plasticity strategies in neurological disease," *Future Neurology*, vol. 13, no. 1, pp. 13–21, 2018.

[30] Q. Zhang, C. Ma, M. Gearing, P. G. Wang, L. S. Chin, and L. Li, "Integrated proteomics and network analysis identifies protein hubs and network alterations in Alzheimer's disease," *Acta Neuropathologica Communications*, vol. 6, no. 1, p. 19, 2018.

[31] A. M. Swomley, S. Förster, J. T. Keeney et al., "Abeta, oxidative stress in Alzheimer disease: evidence based on proteomics studies," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1842, no. 8, pp. 1248–1257, 2014.

[32] S. Geisler, K. M. Holmström, D. Skujat et al., "PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1," *Nature Cell Biology*, vol. 12, no. 2, pp. 119–131, 2010.

[33] T. Ryan, V. V. Bamm, M. G. Stykel et al., "Cardiolipin exposure on the outer mitochondrial membrane modulates α-synuclein," *Nature Communications*, vol. 9, no. 1, p. 817, 2018.

[34] L. D. Osellame and M. R. Duchen, "Quality control gone wrong: mitochondria, lysosomal storage disorders and neurodegeneration," *British Journal of Pharmacology*, vol. 171, no. 8, pp. 1958–1972, 2014.

[35] D. Hughes and G. R. Mallucci, "The unfolded protein response in neurodegenerative disorders – therapeutic modulation of the PERK pathway," *The FEBS Journal*, 2018.

[36] C. Hetz and B. Mollereau, "Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases," *Nature Reviews Neuroscience*, vol. 15, no. 4, pp. 233–249, 2014.

[37] E. A. Moehle, K. Shen, and A. Dillin, "Mitochondrial proteostasis in the context of cellular and organismal health and aging," *The Journal of Biological Chemistry*, 2018.

[38] S. R. Yoshii, C. Kishi, N. Ishihara, and N. Mizushima, "Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane," *The Journal of Biological Chemistry*, vol. 286, no. 22, pp. 19630–19640, 2011.

[39] P. Bragoszewski, M. Turek, and A. Chacinska, "Control of mitochondrial biogenesis and function by the ubiquitin–proteasome system," *Open Biology*, vol. 7, no. 4, article 170007, 2017.

[40] L. Ruan, C. Zhou, E. Jin et al., "Cytosolic proteostasis through importing of misfolded proteins into mitochondria," *Nature*, vol. 543, no. 7645, pp. 443–446, 2017.

[41] J. Avila, J. J. Lucas, M. Perez, and F. Hernandez, "Role of tau protein in both physiological and pathological conditions," *Physiological Reviews*, vol. 84, no. 2, pp. 361–384, 2004.

[42] G. V. W. Johnson and W. H. Stoothoff, "Tau phosphorylation in neuronal cell function and dysfunction," *Journal of Cell Science*, vol. 117, no. 24, pp. 5721–5729, 2004.

[43] F. Biundo, D. del Prete, H. Zhang, O. Arancio, and L. D'Adamio, "A role for tau in learning, memory and synaptic plasticity," *Scientific Reports*, vol. 8, no. 1, p. 3184, 2018.

[44] T. Uchihara, K. Ikeda, and K. Tsuchiya, "Pick body disease and Pick syndrome," *Neuropathology*, vol. 23, no. 4, pp. 318–326, 2003.

[45] K. Ando, K. Tomimura, V. Sazdovitch et al., "Level of PICALM, a key component of clathrin-mediated endocytosis, is correlated with levels of phosphotau and autophagy-related proteins and is associated with tau inclusions in AD, PSP and Pick disease," *Neurobiology of Disease*, vol. 94, pp. 32–43, 2016.

[46] G. W. Roberts, "Immunocytochemistry of neurofibrillary tangles in dementia pugilistica and Alzheimer's disease: evidence for common genesis," *The Lancet*, vol. 332, no. 8626-8627, pp. 1456–1458, 1988.

[47] S. S. Khan and G. S. Bloom, "Tau: the center of a signaling nexus in Alzheimer's disease," *Frontiers in Neuroscience*, vol. 10, no. 31, p. 31, 2016.

[48] D. K. V. Kumar, S. H. Choi, K. J. Washicosky et al., "Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease," *Science Translational Medicine*, vol. 8, no. 340, article 340ra72, 2016.

[49] W. Cerpa, M. Dinamarca, and N. Inestrosa, "Structure-function implications in Alzheimer's disease: effect of Aβ oligomers at central synapses," *Current Alzheimer Research*, vol. 5, no. 3, pp. 233–243, 2008.

[50] K. Beyer, "α-synuclein structure, posttranslational modification and alternative splicing as aggregation enhancers," *Acta Neuropathologica*, vol. 112, no. 3, pp. 237–251, 2006.

[51] J. Diao, J. Burré, S. Vivona et al., "Native α-synuclein induces clustering of synaptic-vesicle mimics via binding to phospholipids and synaptobrevin-2/VAMP2," *eLife*, vol. 2, article e00592, 2013.

[52] C. W. Olanow and P. Brundin, "Parkinson's disease and alpha synuclein: is Parkinson's disease a prion-like disorder?," *Movement Disorders*, vol. 28, no. 1, pp. 31–40, 2013.

[53] A. Alvarsson, D. Caudal, A. Björklund, and P. Svenningsson, "Emotional memory impairments induced by AAV-mediated overexpression of human α-synuclein in dopaminergic neurons of the ventral tegmental area," *Behavioural Brain Research*, vol. 296, pp. 129–133, 2016.

[54] N. Hattori and Y. Mizuno, "Twenty years since the discovery of the parkin gene," *Journal of Neural Transmission*, vol. 124, no. 9, pp. 1037–1054, 2017.

[55] T. Kitada, S. Asakawa, N. Hattori et al., "Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism," *Nature*, vol. 392, no. 6676, pp. 605–608, 1998.

[56] K. M. Doherty, L. Silveira-Moriyama, L. Parkkinen et al., "Parkin disease: a clinicopathologic entity?," *JAMA Neurology*, vol. 70, no. 5, pp. 571–579, 2013.

[57] F. Gonzalez-Lima, B. R. Barksdale, and J. C. Rojas, "Mitochondrial respiration as a target for neuroprotection and cognitive enhancement," *Biochemical Pharmacology*, vol. 88, no. 4, pp. 584–593, 2014.

[58] W. Scheper and J. J. M. Hoozemans, "The unfolded protein response in neurodegenerative diseases: a neuropathological perspective," *Acta Neuropathologica*, vol. 130, no. 3, pp. 315–331, 2015.

[59] V. H. Cornejo and C. Hetz, "The unfolded protein response in Alzheimer's disease," *Seminars in Immunopathology*, vol. 35, no. 3, pp. 277–292, 2013.

[60] A. C. R. G. Fonseca, E. Ferreiro, C. R. Oliveira, S. M. Cardoso, and C. F. Pereira, "Activation of the endoplasmic reticulum stress response by the amyloid-beta 1–40 peptide in brain endothelial cells," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1832, no. 12, pp. 2191–2203, 2013.

[61] C. Supnet and I. Bezprozvanny, "The dysregulation of intracellular calcium in Alzheimer disease," *Cell Calcium*, vol. 47, no. 2, pp. 183–189, 2010.

[62] C. E. Riera and A. Dillin, "Tipping the metabolic scales towards increased longevity in mammals," *Nature Cell Biology*, vol. 17, no. 3, pp. 196–203, 2015.

[63] C. Cantó, L. Q. Jiang, A. S. Deshmukh et al., "Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle," *Cell Metabolism*, vol. 11, no. 3, pp. 213–219, 2010.

[64] R. Raynes, J. Brunquell, and S. D. Westerheide, "Stress inducibility of SIRT1 and its role in cytoprotection and cancer," *Genes & Cancer*, vol. 4, no. 3-4, pp. 172–182, 2013.

[65] J.-G. Lee, J. M. Yon, C. Lin, A. Y. Jung, K. Y. Jung, and S. Y. Nam, "Combined treatment with capsaicin and resveratrol enhances neuroprotection against glutamate-induced toxicity in mouse cerebral cortical neurons," *Food and Chemical Toxicology*, vol. 50, no. 11, pp. 3877–3885, 2012.

[66] M. J. Zhang, Y. Zhou, L. Chen et al., "Impaired SIRT1 promotes the migration of vascular smooth muscle cell-derived foam cells," *Histochemistry and Cell Biology*, vol. 146, no. 1, pp. 33–43, 2016.

[67] Y. Avraham, N. Davidi, M. Porat et al., "Leptin reduces infarct size in association with enhanced expression of CB2, TRPV1, SIRT-1 and leptin receptor," *Current Neurovascular Research*, vol. 7, no. 2, pp. 136–143, 2010.

[68] L. MacPherson and K. Tokatlidis, "Protein trafficking in the mitochondrial intermembrane space: mechanisms and links to human disease," *The Biochemical Journal*, vol. 474, no. 15, pp. 2533–2545, 2017.

[69] C. Park and S. K. Park, "Molecular links between mitochondrial dysfunctions and schizophrenia," *Molecules and Cells*, vol. 33, no. 2, pp. 105–110, 2012.

[70] N. J. Gamo, A. Duque, C. D. Paspalas et al., "Role of disrupted in schizophrenia 1 (DISC1) in stress-induced prefrontal cognitive dysfunction," *Translational Psychiatry*, vol. 3, no. 12, article e328, 2013.

[71] Y. Xu, J. Ren, and H. Ye, "Association between variations in the *disrupted in schizophrenia 1* gene and schizophrenia: a meta-analysis," *Gene*, vol. 651, pp. 94–99, 2018.

[72] M. Niwa, T. Cash-Padgett, K. I. Kubo et al., "DISC1 a key molecular lead in psychiatry and neurodevelopment: No-More *Disrupted-in-Schizophrenia 1*," *Molecular Psychiatry*, vol. 21, no. 11, pp. 1488-1489, 2016.

[73] J. K. Millar, J. C. Wilson-Annan, S. Anderson et al., "Disruption of two novel genes by a translocation co-segregating with schizophrenia," *Human Molecular Genetics*, vol. 9, no. 9, pp. 1415–1423, 2000.

[74] S. Miyata, T. Hattori, S. Shimizu, A. Ito, and M. Tohyama, "Disturbance of oligodendrocyte function plays a key role in the pathogenesis of schizophrenia and major depressive disorder," *BioMed Research International*, vol. 2015, Article ID 492367, 26 pages, 2015.

[75] D. J. Porteous, J. K. Millar, N. J. Brandon, and A. Sawa, "DISC1 at 10: connecting psychiatric genetics and neuroscience," *Trends in Molecular Medicine*, vol. 17, no. 12, pp. 699–706, 2011.

[76] T. Dahoun, S. V. Trossbach, N. J. Brandon, C. Korth, and O. D. Howes, "The impact of *Disrupted-in-Schizophrenia 1* (*DISC1*) on the dopaminergic system: a systematic review," *Translational Psychiatry*, vol. 7, no. 1, article e1015, 2017.

[77] N. J. Brandon, J. K. Millar, C. Korth, H. Sive, K. K. Singh, and A. Sawa, "Understanding the role of DISC1 in psychiatric disease and during normal development," *The Journal of Neuroscience*, vol. 29, no. 41, pp. 12768–12775, 2009.

[78] W. Ratta-apha, A. Hishimoto, K. Mouri et al., "Association analysis of the DISC1 gene with schizophrenia in the Japanese population and DISC1 immunoreactivity in the postmortem brain," *Neuroscience Research*, vol. 77, no. 4, pp. 222–227, 2013.

[79] D. St Clair, D. Blackwood, W. Muir et al., "Association within a family of a balanced autosomal translocation with major mental illness," *The Lancet*, vol. 336, no. 8706, pp. 13–16, 1990.

[80] N. A. Sachs, A. Sawa, S. E. Holmes, C. A. Ross, L. E. DeLisi, and R. L. Margolis, "A frameshift mutation in Disrupted in Schizophrenia 1 in an American family with schizophrenia and schizoaffective disorder," *Molecular Psychiatry*, vol. 10, no. 8, pp. 758–764, 2005.

[81] N. Doi, Y. Hoshi, M. Itokawa, C. Usui, T. Yoshikawa, and H. Tachikawa, "Persistence criteria for susceptibility genes for schizophrenia: a discussion from an evolutionary viewpoint," *PLoS One*, vol. 4, no. 11, article e7799, 2009.

[82] B. Rollins, M. V. Martin, P. A. Sequeira et al., "Mitochondrial variants in schizophrenia, bipolar disorder, and major depressive disorder," *PLoS One*, vol. 4, no. 3, article e4913, 2009.

[83] R. James, R. R. Adams, S. Christie, S. R. Buchanan, D. J. Porteous, and J. K. Millar, "Disrupted in schizophrenia 1 (DISC1) is a multicompartmentalized protein that predominantly localizes to mitochondria," *Molecular and Cellular Neurosciences*, vol. 26, no. 1, pp. 112–122, 2004.

[84] E. Piñero-Martos, B. Ortega-Vila, J. Pol-Fuster et al., "Disrupted in Schizophrenia 1 (DISC1) is a constituent of the mammalian Mitochondrial contact site and Cristae Organizing System (MICOS) complex, and is essential for oxidative phosphorylation," *Human Molecular Genetics*, vol. 25, no. 19, pp. 4157–4169, 2016.

[85] R. Norkett, S. Modi, N. Birsa et al., "DISC1-dependent regulation of mitochondrial dynamics controls the morphogenesis of complex neuronal dendrites," *The Journal of Biological Chemistry*, vol. 291, no. 2, pp. 613–629, 2016.

[86] Y. U. Park, J. Jeong, H. Lee et al., "*Disrupted-in-schizophrenia* 1 (DISC1) plays essential roles in mitochondria in collaboration with Mitofilin," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 41, pp. 17785–17790, 2010.

[87] S. J. Park, S. B. Lee, Y. Suh et al., "DISC1 modulates neuronal stress responses by gate-keeping ER-mitochondria Ca^{2+}

transfer through the MAM," *Cell Reports*, vol. 21, no. 10, pp. 2748–2759, 2017.

[88] H. Eachus, C. Bright, V. T. Cunliffe, M. Placzek, J. D. Wood, and P. J. Watt, "*Disrupted-in-Schizophrenia-1* is essential for normal hypothalamic-pituitary-interrenal (HPI) axis function," *Human Molecular Genetics*, vol. 26, no. 11, pp. 1992–2005, 2017.

[89] M. Niwa, H. Jaaro-Peled, S. Tankou et al., "Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids," *Science*, vol. 339, no. 6117, pp. 335–339, 2013.

[90] D. Arion, J. P. Corradi, S. Tang et al., "Distinctive transcriptome alterations of prefrontal pyramidal neurons in schizophrenia and schizoaffective disorder," *Molecular Psychiatry*, vol. 20, no. 11, pp. 1397–1405, 2015.

[91] B. E. Hjelm, B. Rollins, F. Mamdani et al., "Evidence of mitochondrial dysfunction within the complex genetic etiology of schizophrenia," *Molecular Neuropsychiatry*, vol. 1, no. 4, pp. 201–219, 2015.

[92] V. S. Catts, D. S. Derminio, C.-G. Hahn, and C. S. Weickert, "Postsynaptic density levels of the NMDA receptor NR1 subunit and PSD-95 protein in prefrontal cortex from people with schizophrenia," *npj Schizophrenia*, vol. 1, no. 1, article 15037, 2015.

[93] A. A. Coley and W.-J. Gao, "PSD95: a synaptic protein implicated in schizophrenia or autism?," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 82, pp. 187–194, 2018.

[94] N. S. Kolomeets and N. A. Uranova, "Synaptic contacts in schizophrenia: studies using immunocytochemical identification of dopaminergic neurons," *Neuroscience and Behavioral Physiology*, vol. 29, no. 2, pp. 217–221, 1999.

[95] L. Kung and R. C. Roberts, "Mitochondrial pathology in human schizophrenic striatum: a postmortem ultrastructural study," *Synapse*, vol. 31, no. 1, pp. 67–75, 1999.

[96] N. A. Uranova, D. D. Orlovskaia, O. V. Vikhreva, I. S. Zimina, and V. I. Rakhmanova, "Morphometric study of ultrastructural changes in oligodendroglial cells in the postmortem brain in endogenous psychoses," *Vestnik Rossiĭskoĭ Akademii Meditsinskikh Nauk*, no. 7, pp. 42–48, 2001.

[97] A. Rajasekaran, G. Venkatasubramanian, M. Berk, and M. Debnath, "Mitochondrial dysfunction in schizophrenia: pathways, mechanisms and implications," *Neuroscience & Biobehavioral Reviews*, vol. 48, pp. 10–21, 2015.

[98] G. Anderson, M. Maes, and M. Berk, "Schizophrenia is primed for an increased expression of depression through activation of immuno-inflammatory, oxidative and nitrosative stress, and tryptophan catabolite pathways," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 42, pp. 101–114, 2013.

[99] M. D. Filiou, R. B. Banati, and M. B. Graeber, "The 18-kDa translocator protein as a CNS drug target: finding our way through the neuroinflammation fog," *CNS & Neurological Disorders - Drug Targets*, vol. 16, no. 9, pp. 990–999, 2018.

[100] H. P. Volz, R. Rzanny, G. Röger et al., "Decreased energy demanding processes in the frontal lobes of schizophrenics due to neuroleptics? A ^{31}P-magneto-resonance spectroscopic study," *Psychiatry Research: Neuroimaging*, vol. 76, no. 2-3, pp. 123–129, 1997.

[101] C. N. Hall, M. C. Klein-Flugge, C. Howarth, and D. Attwell, "Oxidative phosphorylation, not glycolysis, powers presynaptic and postsynaptic mechanisms underlying brain information processing," *The Journal of Neuroscience*, vol. 32, no. 26, pp. 8940–8951, 2012.

[102] O. Bergman and D. Ben-Shachar, "Mitochondrial oxidative phosphorylation system (OXPHOS) deficits in schizophrenia: possible interactions with cellular processes," *Canadian Journal of Psychiatry*, vol. 61, no. 8, pp. 457–469, 2016.

[103] S. Akarsu, D. Torun, A. Bolu et al., "Mitochondrial complex I and III gene mRNA levels in schizophrenia, and their relationship with clinical features," *Journal of Molecular Psychiatry*, vol. 2, no. 1, p. 6, 2014.

[104] M. Ayalew, H. le-Niculescu, D. F. Levey et al., "Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction," *Molecular Psychiatry*, vol. 17, no. 9, pp. 887–905, 2012.

[105] O. Robicsek, R. Karry, I. Petit et al., "Abnormal neuronal differentiation and mitochondrial dysfunction in hair follicle-derived induced pluripotent stem cells of schizophrenia patients," *Molecular Psychiatry*, vol. 18, no. 10, pp. 1067–1076, 2013.

[106] P. H. G. M. Willems, J. A. M. Smeitink, and W. J. H. Koopman, "Mitochondrial dynamics in human NADH:ubiquinone oxidoreductase deficiency," *The International Journal of Biochemistry & Cell Biology*, vol. 41, no. 10, pp. 1773–1782, 2009.

[107] H. Brenner-Lavie, E. Klein, R. Zuk, H. Gazawi, P. Ljubuncic, and D. Ben-Shachar, "Dopamine modulates mitochondrial function in viable SH-SY5Y cells possibly via its interaction with complex I: relevance to dopamine pathology in schizophrenia," *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, vol. 1777, no. 2, pp. 173–185, 2008.

[108] A. Bechara, H. Damasio, and A. R. Damasio, "Emotion, decision making and the orbitofrontal cortex," *Cerebral Cortex*, vol. 10, no. 3, pp. 295–307, 2000.

[109] Y. Ouchi and M. Kikuchi, "A review of the default mode network in aging and dementia based on molecular imaging," *Reviews in the Neurosciences*, vol. 23, no. 3, pp. 263–268, 2012.

[110] J. E. Eykelenboom, G. J. Briggs, N. J. Bradshaw et al., "A t(1;11) translocation linked to schizophrenia and affective disorders gives rise to aberrant chimeric *DISC1* transcripts that encode structurally altered, deleterious mitochondrial proteins," *Human Molecular Genetics*, vol. 21, no. 15, pp. 3374–3386, 2012.

Hindawi
Neural Plasticity
Volume 2018, Article ID 8430123, 12 pages
https://doi.org/10.1155/2018/8430123

Review Article

Tumor Necrosis Factor and Interleukin-1β Modulate Synaptic Plasticity during Neuroinflammation

Francesca Romana Rizzo,[1] Alessandra Musella,[2] Francesca De Vito,[1] Diego Fresegna,[1] Silvia Bullitta,[1] Valentina Vanni,[1] Livia Guadalupi,[2] Mario Stampanoni Bassi,[3] Fabio Buttari,[3] Georgia Mandolesi,[2] Diego Centonze,[1,3] and Antonietta Gentile[3]

[1]*Synaptic Immunopathology Lab, Department of Systems Medicine, University of Rome Tor Vergata, 00133 Rome, Italy*
[2]*Synaptic Immunopathology Lab, IRCCS San Raffaele, Via di Val Cannuta 247, 00166 Rome, Italy*
[3]*Unit of Neurology and Unit of Neurorehabilitation, IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, 86077 Pozzilli, Italy*

Correspondence should be addressed to Diego Centonze; centonze@uniroma2.it

Received 16 February 2018; Accepted 28 March 2018; Published 14 May 2018

Academic Editor: Steven W. Johnson

Cytokines are constitutively released in the healthy brain by resident myeloid cells to keep proper synaptic plasticity, either in the form of Hebbian synaptic plasticity or of homeostatic plasticity. However, when cytokines dramatically increase, establishing a status of neuroinflammation, the synaptic action of such molecules remarkably interferes with brain circuits of learning and cognition and contributes to excitotoxicity and neurodegeneration. Among others, interleukin-1β (IL-1β) and tumor necrosis factor (TNF) are the best studied proinflammatory cytokines in both physiological and pathological conditions and have been invariably associated with long-term potentiation (LTP) (Hebbian synaptic plasticity) and synaptic scaling (homeostatic plasticity), respectively. Multiple sclerosis (MS) is the prototypical neuroinflammatory disease, in which inflammation triggers excitotoxic mechanisms contributing to neurodegeneration. IL-β and TNF are increased in the brain of MS patients and contribute to induce the changes in synaptic plasticity occurring in MS patients and its animal model, the experimental autoimmune encephalomyelitis (EAE). This review will introduce and discuss current evidence of the role of IL-1β and TNF in the regulation of synaptic strength at both physiological and pathological levels, in particular speculating on their involvement in the synaptic plasticity changes observed in the EAE brain.

1. Introduction

The recognition that soluble mediators of the immune system, namely, cytokines, are constitutively expressed in the central nervous system (CNS) has completely changed our vision of brain functioning [1]. Indeed, the study of the neuroimmune connection is an extraordinary field of research, having strong implications for understanding physiological and pathological conditions [2, 3]. The proinflammatory cytokines IL-1β and TNF, released by resident cells of the immune lineage, have been proven to physiologically modulate synaptic plasticity, mainly the Hebbian synaptic plasticity and the synaptic scaling, in different brain areas such as the cortex, striatum, and hippocampus [4, 5].

TNF is a proteolytically cleaved transmembrane protein whose activity is performed through TNF receptor type 1 (TNFR1) and type 2 (TNFR2) [6]. In physiological state, the glial pathway that regulates TNF release is itself controlled by TNF [7], but when the balanced system is strongly disturbed, the homeostatic mechanism fails. This

cytokine is an important regulator of synapse function implicated in synaptic transmission and homeostatic synaptic scaling [8, 9].

IL-1β is the product of the proteolytic cleavage of its mature form pro-IL-1β. IL-1β exerts its biological action by binding to IL-1 receptor type 1 (IL-1RI), competing with IL-1 receptor antagonist (IL-1ra), the endogenous inhibitor of IL-1β [10]. A bulk of data indicate that IL-1β is necessary for synaptic mechanisms, like LTP, underlying learning and memory [4].

When brain levels of cytokines significantly rise as a result of an immune challenge, the scenario about the neuroimmune connection deeply changes. Under this condition, IL1-β and TNF, whose basal activity is necessary for maintenance of proper synaptic plasticity, start to exert noxious effects on synaptic transmission. Interestingly, the mechanisms underlying the shift from a healthy immune function to a detrimental one are poorly understood [4]. However, during chronic neuroinflammatory and neurodegenerative diseases, like Alzheimer's disease (AD) and multiple sclerosis (MS), changes in synaptic plasticity due to the effects of these cytokines might also be an adaptive mechanism occurring to compensate for synaptic and/or neuronal loss.

While the physiological regulation of synaptic plasticity by TNF and IL-1β has been widely investigated, the involvement of such cytokines in synaptic plasticity alterations associated with neurological disorders is merely speculative and relies only on few studies on animal models. In this respect, due to the recognized pathogenic role of inflammation in MS, many clinical and preclinical studies have been performed to address the role of TNF and IL-1β in the modulation of synaptic plasticity [11].

Moving from a brief introduction on the key properties of both synaptic scaling and LTP, the present review summarizes the main evidence for the physiological and pathological functions of IL-1β and TNF and their cellular sources in the brain in regulating synaptic plasticity. Moreover, we will discuss data from EAE, animal model of MS, which support a role for both cytokines in synaptic changes and adaptations during neuroinflammation.

2. Synaptic Plasticity

Changes in synaptic strength and brain network activity occur either as an adaptive response to environmental stimuli or as a consequence of local insult affecting single or multiple neurons. From development to ageing, several forms of synaptic plasticity coexist and cooperate to maintain proper synaptic transmission and to keep homeostasis in brain circuits. Among others, Hebbian plasticity and synaptic scaling are the most relevant form of synaptic plasticity, whose induction and maintenance underlie not only experience-dependent mechanisms, like memory processes, but also pathological conditions of neuronal perturbations [12]. As reported in the following sections, LTP and synaptic scaling result in the strengthening of the glutamatergic transmission and, although sharing some features, are intrinsically different in nature.

2.1. LTP: Properties and Biological Relevance. LTP is a form of synaptic plasticity consisting in long-lasting increase in the synaptic strength between pre- and postsynaptic neurons. It is artificially induced through electrophysiological protocols of high-frequency stimulation [12]. LTP can be experimentally induced in virtually all the excitatory synapses in the brain. However, most of our knowledge about the molecular mechanisms of LTP arises from studies in the cornu ammonis area 1 (CA1) region of the hippocampus, where the main form of LTP is dependent on N-methyl-D-aspartate receptor (NMDAR) activity. Decades of experimental research have led to some key concepts about LTP nature.

Briefly, LTP is (i) cooperative, since it requires the coincident activation of a critical number of synapses; (ii) associative, in a way that weak input, involving a small number of synapses, can be strengthened by the association with a strong input, coming from a larger number of synapses; and (iii) input-specific, because only activated synapses on the postsynaptic neuron are recruited during LTP. This implies that LTP occurs in case of coincidence activity between pre- and postsynaptic neurons in a positive feedback. Indeed, to be triggered, LTP first needs the increased conductance through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), which in turn activate postsynaptic NMDARs (early phase of LTP) [13]. Glutamate massively released from presynaptic terminal binds both AMPARs and NMDARs. However, the latter are activated only once Mg^{2+} is removed from the central pore of NMDAR, and this is achieved by AMPAR-mediated membrane depolarization. Subsequent Ca^{2+} influx through NMDAR channel triggers intracellular signaling cascade necessary for synaptic plasticity [14]. Furthermore, to be persistent over time, LTP requires de novo protein synthesis, necessary for storage of information: the late phase of LTP implies structural changes in postsynaptic density (PSD), which is linked to the induction of immediate early genes (IEG) and the synthesis of proteins like *Arc-Arg*, which stabilizes F-actin filaments and regulate AMPAR membrane expression [15]. On a functional level, compelling studies based on behavioural tests and electrophysiology have clearly linked LTP in the hippocampus with learning [16, 17] and memory [18–20].

Based on subunit composition (NR2A versus NR2B) and localization at synapse (synaptic or extrasynaptic), signaling through NMDAR can induce either neuroprotection [21] or neurotoxicity [22]. Although the causal link between synaptic plasticity and neuroprotection is still not fully elucidated, growing data point to NMDAR-dependent LTP as prosurvival strategy [23], aimed at recovering activity in those neurons, which have lost part of their synaptic inputs.

2.2. Il-1β Is the Main Immune Trigger of LTP in Physiological Condition. During physiological neuronal activity, several factors have been shown to induce LTP, including the brain-derived neurotrophic factor (BDNF) [24, 25]. However, in the past decades, unexpected interactions between environmental/psychological experiences, immune system, and brain activity have been highlighted, providing evidence for physiological control of learning and memory mediated

by the immune system [4]. Research in this field has focused on the effect of cytokines on the induction and maintenance of hippocampal LTP, indicating that IL-1β, rather than TNF, is the main immune player in LTP regulation. Indeed, mice with genetic deletion of components of TNF signaling showed unaltered hippocampal LTP [8, 26].

After the first observation that LTP induction is physiologically followed by IL-1 gene expression [27], several studies based on genetic knockdown [28] or *in vitro* and *in vivo* pharmacological blockade of IL-1R [29, 30] have indicated the necessary role of IL-1β in LTP induction and maintenance. LTP in CA1 region of IL1-R KO mice is absent [28], and intracerebroventricular administration (ICV) of IL-1ra significantly affected both the initial potentiation and the maintenance of LTP [30]. The critical role of IL-1β in the maintenance of LTP was demonstrated in *in vitro* experiments: application of IL-1ra 30 min after LTP induction rescued basal synaptic transmission. A putative mechanism by which IL-1β modulates LTP involves changes in Ca^{2+} conductance through NMDAR [31]. Noteworthy, *in vivo* manipulations of IL1-β signaling were associated with disturbances in memory and learning of mice: compared to wild-type (WT) IL-1R KO mice showed slower rate of learning in the spatial memory paradigm [28], impaired contextual but normal auditory-cued fear conditioning in water *T*-maze paradigm [32]. Moreover, ICV injection of IL-1ra induced similar behavioural phenotype [32]. Overall, these data point to IL-1β as the main immune player involved in LTP induction and maintenance as well as memory and learning processes (Figure 1(a)).

2.3. Synaptic Scaling: Properties and Biological Relevance. A form of synaptic plasticity, profoundly different from LTP, is the synaptic scaling. The synaptic scaling acts to keep the postsynaptic weights of excitatory synapses around a firing rate set point. Therefore, by definition, synaptic scaling is a homeostatic form of synaptic plasticity, triggered to globally reduce (downscaling) or increase (upscaling) the excitatory drive during chronic inactivity or hyperactivity [33]. Persistent and uncontrolled Hebbian plasticity or reduced number of synapses for pathological reasons can induce synaptic scaling. However, our knowledge on how Hebbian plasticity and synaptic scaling are temporally linked to each other and mechanistically intermingled is still in its infancy [34]. In contrast to LTP, synaptic scaling (i) acts in a negative feedback, (ii) is not input-specific, as it can spread to multiple synapses, and, more interestingly, (iii) mainly relies on AMPAR functioning. Indeed, the excitatory synaptic transmission can be strengthened or weakened by slowly increasing or reducing the number of clustered AMPAR on postsynaptic membrane, respectively [33, 35]. This is a global effect, involving all the synapses of a postsynaptic neuron. As a result of these changes in AMPAR membrane insertion or removal, the conductance of AMPAR is increased or reduced and the PSD area is changed accordingly [36, 37]. Synaptic scaling is associated with the induction or inhibition of Arc/Arg gene [38, 39], leading to increased or reduced rate of surface AMPAR endocytosis with the consequent reduction or enhancement of membrane-expressed AMPARs. Therefore, being involved in both Hebbian plasticity and synaptic scaling, Arc protein seems to play a crucial role in regulating synaptic plasticity [40]. Homeostatic synaptic plasticity has been well documented *in vivo* in visual cortex during experience-deprivation paradigms [41, 42] or in sleep/awake states [31, 43].

2.4. TNF Is the Main Immune Trigger of Synaptic Scaling in Physiological Condition. Similar to Hebbian plasticity, synaptic scaling is sensitive to the regulation by molecules of the immune system. If IL-1β is definitively associated with constitutive Hebbian plasticity, TNF is invariably associated with synaptic scaling [44, 45]. The first and foremost evidence that TNF is able to alter normal synaptic function was demonstrated in a study where a twofold increase expression of AMPARs on the plasma membrane was detected after an exposure of cultured hippocampal neurons to TNF at different concentrations (0.6–60 nM acute exposure) [9]. Additionally, application of TNFR1 antibody decreased GluR1 surface expression in hippocampal neurons [46], indicating the necessary and constitutive role of TNF in regulating AMPAR membrane insertion and in modifying synaptic strength. Notably, the seminal paper by the Malenka group highlighted the role of glial TNF in inactivity-induced synaptic scaling [8]. Blockade of TNF signaling during prolonged tetrodotoxin (TTX) treatment prevented scaling up of excitatory synapses in hippocampal neurons. Moreover, neurons from TNF KO mice grown on glia from WT mice did show synaptic scaling, while neurons from WT mice grown on glia from TNF KO mice did not [8]. Similar findings were obtained in neurons of the visual cortex [26]. More recently, TNF has been causally involved in size increase of spines close to branches that had recently undergone spine loss [47].

Curiously, in contrast to hippocampal and cortical neurons, TNF was shown to downregulate AMPAR membrane expression in striatal neurons, raising the possibility that in this brain region it exerts an adaptive role to limit the strength of synaptic drive from the cortex [48]. Of note, the physiological role of TNF in inducing synaptic scaling has been well documented *in vivo* in the visual cortex of animals subjected to chronic monocular deprivation [26, 47, 49], further supporting the idea that TNF is a critical player in activity-dependent synaptic adaptations (Figure 2(a)).

3. Synaptic Plasticity: Synaptic Scaling and LTP during Neuroinflammation

Cells of both the innate (resident microglia and astroglia) and the adaptive (T-cells) immune response have been clearly implicated in the physiological regulation of mood, learning, memory, and experience-dependent synaptic activity [50, 51]. Any changes in brain homeostasis that imply microglia and astroglia activation and/or T-cell infiltration trigger an inflammatory response, which is a mechanism of brain defence and can affect synaptic plasticity. During neuroinflammation, activated microglia, astroglia, and infiltrating lymphocytes specifically interact with neurons and influence

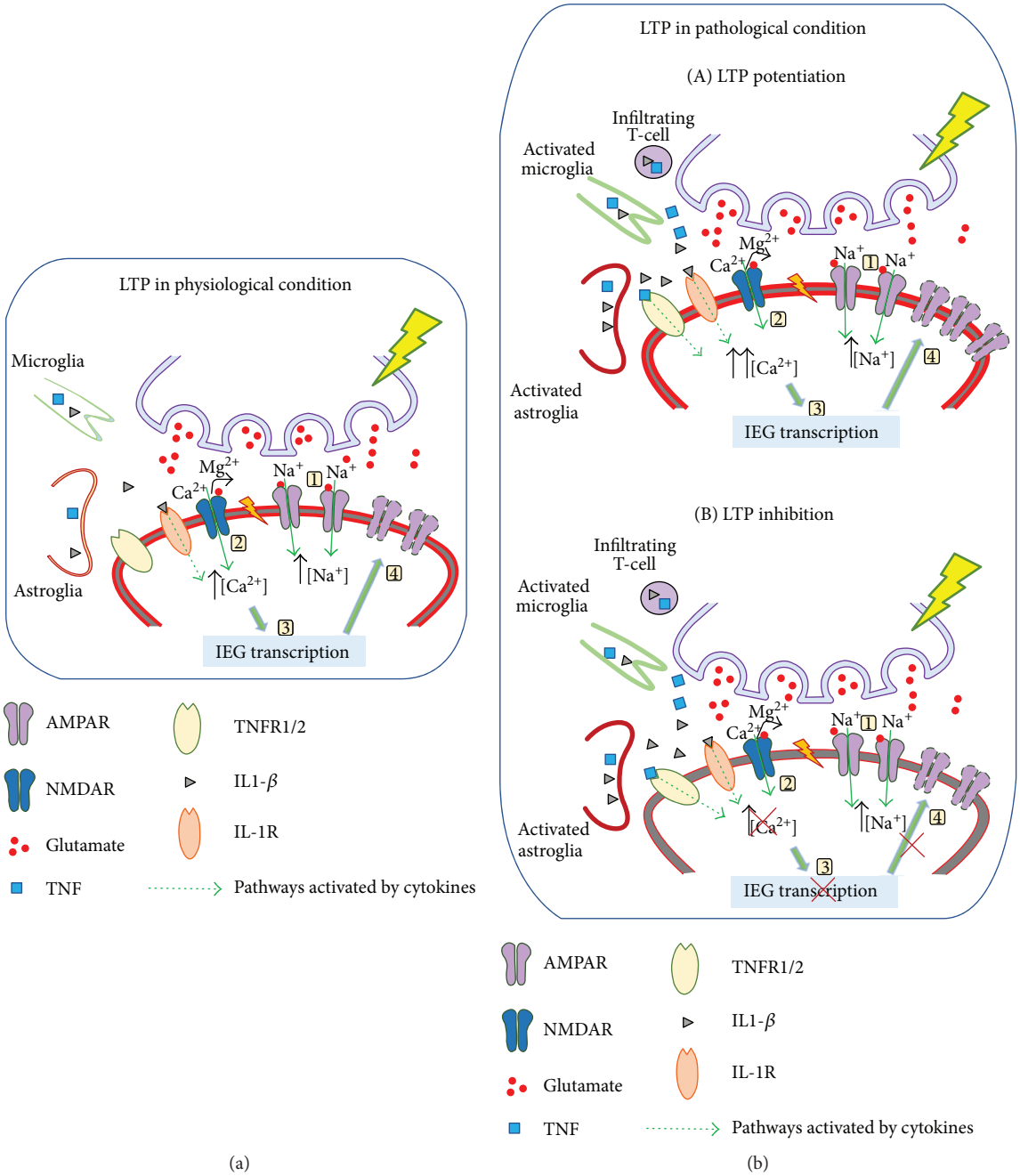


Figure 1: LTP regulation in physiological and pathological states. The triggering of LTP implies coincident pre- and postsynaptic neuron activation. Strong glutamate release from presynaptic terminal promotes membrane depolarization mediated by Na^+ influx through AMPARs (1), which in turn activates NMDARs by means of Mg^{2+} expulsion from NMDAR pore, thus allowing Ca^{2+} influx (2). Next, the increase of intracellular Ca^{2+} concentration activates a cascade of events involving several molecular players and leads to the induction of IEGs (3), such as Arc/Arg, necessary for structural (increased stability and size of dendritic spines) and functional changes of the PSD and the synthesis and insertion of AMPARs in membrane (4). Physiological levels of IL-1β released by both microglia and astroglia contribute to LTP phenomenon (a). During neuroinflammatory disorders (b), activated resident (microglia and astroglia) and infiltrating T-cells strongly release TNF and IL-1β, thus generating two possible outcomes of synaptic changes (A, B). As illustrated in the figure, LTP can be either potentiated or prevented through the action of TNF and IL-1β interfering with the pathways controlling the molecular and structural synaptic changes occurring during LTP.

their survival either in a positive or in a negative direction depending on the pathologic context, by releasing cytokines [52]. Therefore, we will review current findings about the role of TNF and IL-1β in animal models of neuroinflammatory conditions and of neurodegenerative diseases, the latter characterized by chronic inflammation.

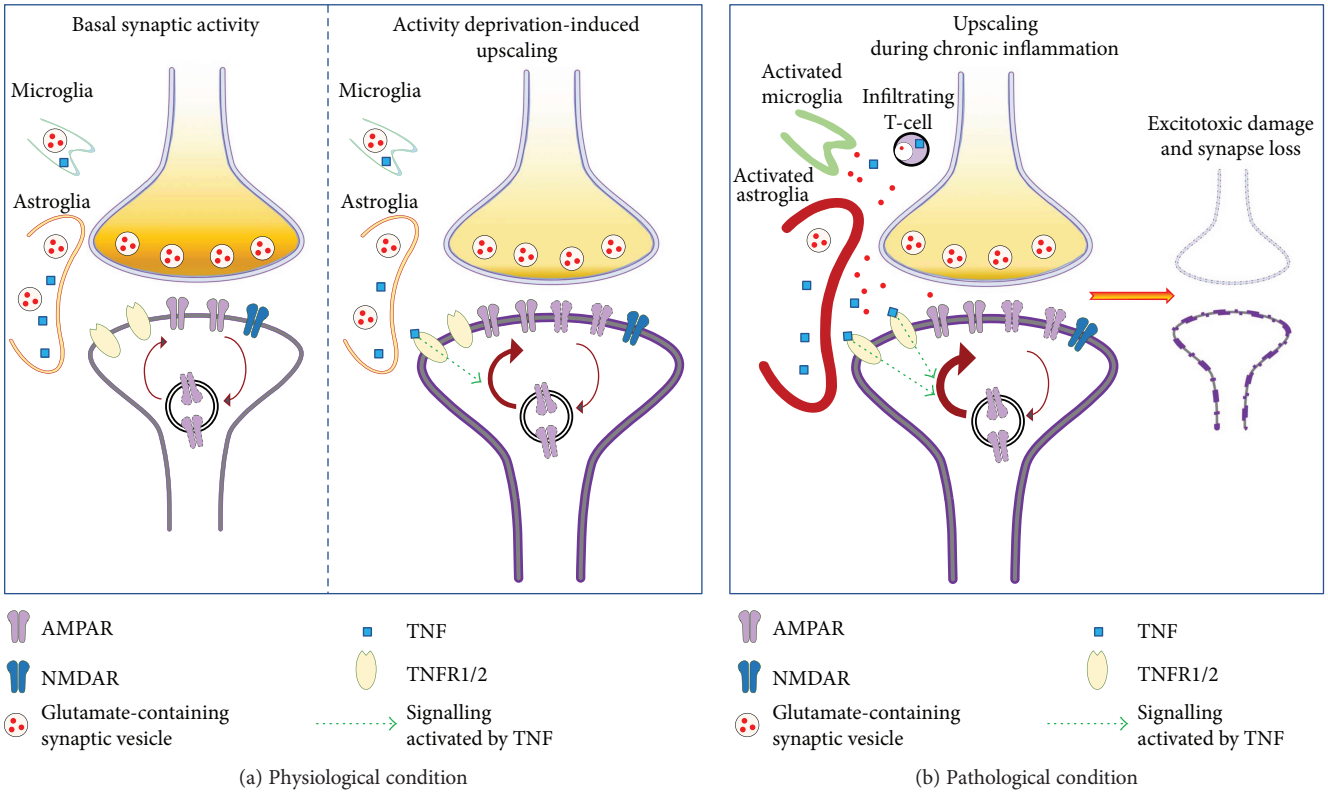


Figure 2: Synaptic upscaling in response to physiological and pathological stimuli. (a) In a physiological state, during basal synaptic activity, AMPARs undergo constant cycles of membrane insertion and removal on postsynaptic neuron. When the synaptic strength driven by the presynaptic terminal is reduced, TNF, released by astroglia, activates a molecular mechanism leading to transient improved insertion of AMPARs on postsynaptic membrane. (b) During acute or chronic neuroinflammation, TNF, massively released by activated microglia and astroglia as well as infiltrating T-cells, indefinitely upregulates the mechanism of membrane AMPAR insertion. In parallel, inflammation affects physiological mechanisms of glutamate clearance at synaptic cleft. This together with enhanced glutamate release from glial cells over activates AMPARs, thus contributing to induce excitotoxic mechanisms and synaptic loss.

3.1. Synaptic Plasticity: The Role of TNF during Neuroinflammation. Experimental paradigms of deafferentiation-induced homeostatic plasticity have highlighted that signaling activated by TNF plays a role in the long-term maintenance of synaptic scaling. In hippocampal slices that underwent denervation from entorhinal cortex (EC), glial TNF increased only after 3-4 days postlesion, while the enhancement of excitatory transmission in dentate gyrus (DG) granule cells was observed already after 1-2 days postlesion [53]. Moreover, in the same experimental model of denervation followed by neuroinflammation, it was shown that TNF was involved in LTP maintenance by binding to both TNFR1 and TNFR2 [54].

As already mentioned, TNF exerts different physiological effects in the hippocampus and the striatum [8, 48], and several data suggest that TNF massively released during neuroinflammation may have brain area-specific effects, as well. Accordingly, it has recently been shown that TNF of microglial origin impairs hippocampal LTP in CA1 region, whereas it improves LTP at C-fiber synapses in spinal dorsal horn in a model of peripheral nerve injury, which is associated with memory deficits and pain [55]. Another study on the same model analysed the effect of TNF on hippocampal LTP at CA3-CA1 synapses: LTP was impaired in injured animals and the same effect was observed after intrahippocampal or ICV injection of TNF in healthy mice [56]. These outstanding *in vivo* findings corroborate data from *in vitro* acute application of TNF. It has been shown that TNF impairs dose-dependently LTP induction or maintenance in the hippocampus, by preventing the initial reduction of potentiation (early phase of LTP) and by inhibiting the late increased potentiation (late phase of LTP) [57, 58]. Interestingly, pretreatment of hippocampal slices with TNF after hypoxia improved LTP in the DG [59]. In line with this, by means of transgenic mice overexpressing TNF, other researchers have demonstrated that chronic exposure to TNF potentiates LTP in CA1 region [60] (Figures 1(b) and 2(b)).

3.2. Synaptic Plasticity: The Role of IL-1β during Neuroinflammation. Several lines of data consistently indicate that increased levels of IL-1β inhibit LTP in CA1, CA3, and DG of the hippocampus, either after *in vitro* application of the cytokine or *in vivo* ICV delivery [58, 61–63]. IL-1β has been shown to dose-dependently affect Ca^{2+} conductance through NMDARs, being able to improve or inhibit Ca^{2+} influx at low or high concentration, respectively [31]. Moreover, increased brain levels of IL1-β may inhibit LTP

maintenance by interfering with BDNF signaling cascades, thereby impairing the formation of F-actin in dendritic spines [64]. Among others, these are the putative mechanisms by which IL-1β improves or impairs LTP induction.

Regarding *in vivo* studies, stress induced by social isolation and age in rats has been associated with LTP impairment in the DG in correlation with IL-1β levels [65]. In animal model of seizure, which is associated with induction of proinflammatory cytokines, hippocampal LTP inhibition and memory deficits were recovered by treatment with anakinra, the human receptor antagonist of IL1-β, and not by IL-6 and TNF inhibitors [66]. Likewise, in a model of septic encephalopathy, preincubation of hippocampal slices from septic mice with Il-1ra before the stimulation was found to recover LTP deficiency associated with such pathological condition [67]. Furthermore, in obese mice, intrahippocampal delivery of IL-ra rescued LTP deficiency as well as cognitive impairments at *Y*-maze test [68] (Figure 1(B)).

3.3. Synaptic Plasticity: The Role of TNF and IL-1β during Neurodegeneration. Increasing interest has been paid to the role of IL-1β and TNF during age-related pathological conditions, like AD, since their levels have been found increased in the cerebrospinal fluid (CSF) of these patients [69]. Brain ageing is associated with increased basal levels of cytokines and susceptibility to neuroinflammation, accounting for memory and learning deficits [70]. Of note, neuroinflammation in old people is proposed to contribute to the neurodegenerative cascade typical of AD, namely, β-amyloid- (Aβ-) dependent synaptic pathology [71, 72]. Indeed, in line with the aforementioned hypothesis of the inhibitory effect of elevated levels of TNF on LTP in the hippocampus, it has recently shown that in a transgenic mouse model of AD, the peripheral inhibition of the soluble form of TNF attenuates Aβ load, cognitive, and LTP deficits [73]. Regarding Il-1β involvement in synaptic pathology associated with AD, IL1-ra treatment partially attenuated $A\beta_{1-40}$ impairment of LTP in the CA1 of hippocampus [30], supporting previous findings suggesting that $A\beta_{1-40}$ induces the release of IL-1β [74]. However, in another study, it was proposed that Aβ toxicity was TNF-dependent, since the suppression of LTP induced by Aβ was prevented by pharmacological inhibition of TNF and absent in mice lacking the TNFR1 [75]. These data highlight that cytokines play a crucial role in mediating Aβ synaptotoxicity and mechanisms of memory loss during ageing [72].

Altogether, these findings indicate the detrimental role of high concentrations of TNF and IL-1β in both forms of synaptic plasticity during neuroinflammatory and neurodegenerative diseases. It is worth noting that, to date, the occurrence of synaptic scaling in animal models of neurodegenerative diseases has not been addressed. However, it might be hypothesized that in a condition of chronic exposure to high levels of TNF in response to prolonged neuronal activity blockade [8], a kind of super upscaling occurs. This event together with inflammation-impaired mechanisms of glutamate homeostasis regulation subsequently contributes to excitotoxic damage [76, 77] (Figure 2(b)). This issue needs further investigation.

4. Evidence of Synaptic Plasticity Perturbations in the Animal Model of MS, EAE

MS is the prototypical neuroinflammatory disorder, initiated by an autoimmune T-cell-mediated reaction against myelin antigen. Demyelination and neurodegeneration are pathological hallmarks of the brains of MS patients and of its animal model EAE [78]. It is worth noting that the synaptic compartment is early perturbed in MS and EAE, and that inflammation is the main trigger of synaptic damage [79]. Such synaptopathy, caused by inflammatory mediators, has been proposed to cogently contribute to cognitive deficits [79], mood disturbances [80], and disability [81] in MS. In particular, cortical Hebbian synaptic plasticity, that is, LTP and LTD, has been explored in MS patients, by means of transcranial magnetic stimulation (TMS) protocols and correlated with the levels of IL-1β and TNF [11, 81]. In MS, LTP is favored over LTD and LTP potentiation correlates with IL-1β levels in the cerebrospinal fluid (CSF) of MS patients [82]. Moreover, TNF-enriched CSF from MS patients applied to murine brain slices induced the potentiation of glutamatergic transmission, in a way resembling synaptic scaling [83]. Parallel studies on EAE model have confirmed such alterations in basal synaptic transmission and plasticity, providing evidence for a direct involvement of TNF and IL-1β in correlation with microglia and astroglia activation and T-cell infiltration [84].

4.1. The Role of TNF on Synaptic Activity in EAE. It is properly recognized that in the gray matter of EAE and MS brains, the levels of TNF are severely high [83, 85, 86]. The synaptic activity in EAE mice has been largely investigated by our group. The impact of TNF on synaptic strength has been studied by means of both electrophysiological techniques and biochemical assays. In particular, we observed alterations of frequency and duration of spontaneous and miniature glutamatergic events (sEPSCs, mEPSCs), reporting an increase of both parameters in striatal neurons of EAE mice. Notably, these changes were already evident before the clinical manifestations of the disease [85, 86]. At this stage of the disease, TNF levels have been found increased in EAE striatum [86], raising the possibility that it could be the responsible of such glutamatergic transmission enhancement with an involvement of AMPAR trafficking [8]. Indeed, biochemical assays in synaptosomal preparation of EAE striatum revealed increased expression of GluR1 subunit of AMPAR and its phosphorylation at the Ser845 residue indicative of enhanced AMPAR membrane insertion. Moreover, Arc/Arg mRNA was downregulated in the whole striatum [85]. Together with electrophysiological data, these results are suggestive of synaptic upscaling in the EAE brain [39, 77, 87–89].

The casual link between TNF and enhanced glutamate transmission in EAE striatum was demonstrated by *in vivo* and *in vitro* experiments. Electrophysiological recordings of slices from EAE mice that received ICV treatment with anti-TNF antibody showed the rescue of glutamatergic transmission alteration, while ICV administration of TNF in control mice induced the same enhancement of glutamatergic

transmission observed in EAE [86]. Moreover, *in vitro* experiments of long period of incubation (3 h) of control slices with high concentration of TNF (0.6 μM) mimicked the effects of EAE [85]. Such result is apparently in contrast with findings from Lewitus and colleagues (2014), who found that TNF reduced the amplitude of sEPSC and the membrane insertion of AMPAR in the striatum [48]. However, time (1 h) and concentration of TNF (100 ng/ml) in their experimental settings were remarkably different from ours, likely explaining the different *in vitro* results. Of note, the "strong" *in vitro* treatment that we used closely reproduced the EAE glutamatergic transmission potentiation, likely mimicking the effect of chronic exposure of synapses to high levels of TNF. Finally, we confirmed that glial TNF is responsible for the striatal upscaling in EAE: *in vitro* activated microglial cell line applied to control slices increased the duration of glutamatergic spontaneous events and this effect was reversed in the presence of a TNF antibody [85].

The strengthening of glutamatergic transmission in EAE striatum was persistent throughout the disease course. At later stages of the disease, in which inflammation turns into a chronic state, some neurodegenerative features have been described, such as the loss of parvalbumin-positive interneurons (PV+) and of dendritic spines in the gray matter of EAE mice [85, 90], suggesting that inflammatory chronic elevation of TNF may turn physiological upscaling into uncontrolled upscaling, leading to excitotoxic synaptic and neuronal damage [76, 85].

An elegant study published by Habbas and colleagues has demonstrated the involvement of local TNF release in the DG of EAE mice in the strengthening of excitatory transmission in correlation with memory deficits in these mice [91]. The authors found that the excitatory transmission at EC-DG synapses is increased in an astrocytic TNFR1-dependent manner. Indeed, to demonstrate the necessary role of TNF in the potentiation of glutamatergic transmission in circuit involved in contextual learning and memory, they used conditional KO mice for TNFR1 in glial cells. Slices taken from these mice incubated with increasing concentrations of TNF did not show glutamatergic transmission alterations, while the reexpression of TNFR1 in astrocytes rescued the sensitivity to TNF synaptic effect. Moreover, by inducing EAE in this conditional KO mice, they demonstrated that cognitive failure and potentiation of EC-DG glutamatergic transmission are dependent on TNF signaling through astrocytic TNFR1 [91]. Although not fully investigated, along with presynaptic effect of TNF, the authors also found an increase of mEPSC amplitude, consistent with postsynaptic effects of TNF. These results further highlight the role of TNF in synaptic pathology associated with EAE.

4.2. The Role of IL1-β on Hippocampal Synaptic Plasticity in EAE. IL-1β is clearly related to synaptic plasticity rather than upscaling mechanisms in both physiological and pathological conditions (see Sections 2.2 and 3.2). IL-1β is essentially involved in the modulation of LTP form of plasticity in EAE mice. In particular, we showed that EAE mice exhibited a favored LTP induction over LTD in the CA1 area of hippocampus. This effect correlated with increased levels of IL-1β and was reversed by chronic ICV treatment with IL-1ra [82, 92]. Moreover, preincubation of IL-1β on hippocampal slices was able to alter LTP, by inducing a greater potentiation in comparison to control condition and also an inhibition of LTD in CA1 [92]. Of note, any changes in input-output curves as well as in AMPA/NMDA ratio in CA1 were observed in EAE, thus indicating a specific effect on synaptic plasticity induction and maintenance without significant alterations of glutamatergic basal transmission. Based on the above results, we speculated that this effect of EAE on Hebbian forms of plasticity could be the consequence of the reduction of GABAergic inhibition, caused by loss of PV+ GABAergic interneurons [92]. We also demonstrated that *in vitro* activated microglia incubated with control slices inhibited the GABAergic transmission, and that this effect was reversed in the presence of IL1-ra. Considering the role of infiltrating T-lymphocytes in EAE/MS pathology, we tested the hypothesis that these cells, by releasing IL-1β [93], might contribute to hippocampal changes in synaptic activity. Experiments carried out with incubation of T-lymphocytes taken from EAE spleen and placed onto hippocampal control slices promoted LTP over LTD, in a way resembling the LTP recorded from EAE slices, and reduced the GABAergic tone [82]. Thus, EAE-specific T-lymphocytes, by suppressing GABAergic transmission in an IL-1β-dependent manner, were likely able to lower the threshold of LTP induction. We concluded that IL-1β was involved in both the modulation of basal GABAergic synaptic transmission, supposed to precede and contribute to the loss of GABAergic interneurons, and in the potentiation of synaptic plasticity as an adaptive/reparative mechanism.

However, apparently, contrasting data have been reported in literature about hippocampal LTP in EAE [94–96]. Di Filippo and colleagues found that hippocampal LTP is impaired in EAE induced in Biozzi ABH mice, and that IL-1β replicates such alteration in *in vitro* experiments. Although not demonstrating a direct link with IL-1β, the same authors associated LTP inhibition in EAE to hippocampal-dependent memory defects observed in EAE mice: both behavioural and synaptic alterations in EAE were recovered by suppressing microglia activation by means of peripheral injection of minocycline [95]. Despite the lack of a direct link with IL-1β, other studies demonstrated the impairment of hippocampal LTP during the course of EAE [97–99]. In particular, in the paper by Kim et al. (2012), LTP in CA1 region was affected by EAE at both early and late time points and in connection with spatial memory defects [97], while in the investigation by Novkovic et al. (2015), both LTP and cognition were impaired only at late time points [98]. Interestingly, Planche and colleagues correlated impairment of LTP in the DG and of contextual fear memory response in EAE mice with microglia activation, since peripheral administration of minocycline was able to recover both synaptic and behavioural defects [100]. Conversely, Prochnow et al. (2013) investigated presynaptic properties in CA1 hippocampal EAE mice slices reporting a reduction in paired pulse facilitation in comparison with control mice, but no differences were found in LTP induction [96].

As already discussed elsewhere [11, 101], several factors, like EAE model (mice/rats, immunization procedure), different stimulation protocols of LTP, and time points of recordings, which are severely affected by the inflammatory bulk, may explain the contrasting results that have been described in the literature. Even if clear conclusions about synaptic plasticity in CA1 area of EAE hippocampus cannot be drawn, the above data strongly implicate IL-1β in synaptic rearrangements during the course of chronic neuroinflammation.

5. Conclusions

LTP and synaptic scaling serve as fine-tuning regulators of synaptic strength in the healthy brain and are regulated by IL-1β and TNF, which, physiologically act "on demand," being released in an activity-dependent manner. Interference with these mechanisms can bring to aberrant expression of both forms of synaptic plasticity.

Data discussed in the present review clearly indicate that IL-β is largely involved in the constitutive regulation of Hebbian plasticity, while TNF is the main player in homeostatic plasticity. However, such dichotomy is only partially preserved during sustained neuroinflammation. Indeed, although limited, data in literature indicate that in both acute (i.e., ICV injection of cytokine) and chronic (i.e., EAE and AD transgenic model) paradigms of brain inflammation, IL-1β is still linked to LTP expression, whereas TNF seems to affect both LTP and synaptic scaling (Figures 1 and 2). To this respect, it should be noted that the biological relevance of an altered expression of synaptic plasticity has been poorly explored in animal models of neurodegenerative diseases, with the exception of MS. In this context, evidence suggestive of an aberrant upscaling mediated by TNF and leading to excitotoxic neurodegeneration has been shown in the striatum of EAE mice. Moreover, TNF-induced glutamatergic transmission enhancement in the DG has been proposed as the synaptic counterpart of cognitive defects in EAE. Regarding Hebbian plasticity, although contrasting, several lines of evidence indicate that LTP expression in EAE is altered in an IL-1β-dependent manner. According to these results, aberrant hippocampal synaptic plasticity may contribute either to cognitive impairment or to minimize neuronal and synaptic damage. This issue needs further investigations and may include the effects of other cytokines, like Interleukin-6 (IL-6), and immune molecules, such as major histocompatibility complex type 1 (MHCI), already found to modulate synaptic plasticity [4]. Moreover, the fact that cytokine pathways are highly intermingled, implying mutual regulation lays the ground for a better understanding of the complex interaction between immune system and synaptic activity during the course of chronic neuroinflammation.

Abbreviations

TNF:	Tumor necrosis factor
IL-1β:	Interleukin-1β
LTP:	Long-term potentiation
MS:	Multiple sclerosis
EAE:	Experimental autoimmune encephalomyelitis
CNS:	Central nervous system
TNFR1, 2:	TNF receptor type 1 and type 2
IL-1RI:	IL-1 receptor type 1
IL-1ra:	IL-1 receptor antagonist
AD:	Alzheimer's disease
CA1, 3:	Cornu ammonis area 1, 3
NMDAR:	N-Methyl-D-aspartate receptor
AMPAR:	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
PSD:	Postsynaptic density
IEG:	Immediate early genes
NR2A, B:	N-Methyl D-aspartate receptor subtype 2A, B
BDNF:	Brain-derived neurotrophic factor
ICV:	Intracerebroventricular administration
WT:	Wild-type
KO:	Knockout
GluR1:	AMPA receptor subunit 1
TTX:	Tetrodotoxin
EC:	Entorhinal cortex
DG:	Dentate gyrus
LTD:	Long-term depression
TMS:	Transcranial magnetic stimulation
CSF:	Cerebrospinal fluid
sEPSCs, mEPSCs:	Spontaneous and miniature glutamatergic events
PV+:	Parvalbumin-positive interneurons
GABA:	γ-Aminobutyric acid
IL-6:	Interleukin-6
MHCI:	Major histocompatibility complex type 1.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Acknowledgments

Antonietta Gentile was supported by the "Umberto Veronesi Foundation" fellowship.

References

[1] J. McAfoose and B. T. Baune, "Evidence for a cytokine model of cognitive function," *Neuroscience & Biobehavioral Reviews*, vol. 33, no. 3, pp. 355–366, 2009.

[2] M. Schwartz and A. Deczkowska, "Neurological disease as a failure of brain–immune crosstalk: the multiple faces of neuroinflammation," *Trends in Immunology*, vol. 37, no. 10, pp. 668–679, 2016.

[3] M. Di Filippo, P. Sarchielli, B. Picconi, and P. Calabresi, "Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders," *Trends in Pharmacological Sciences*, vol. 29, no. 8, pp. 402–412, 2008.

[4] R. Yirmiya and I. Goshen, "Immune modulation of learning, memory, neural plasticity and neurogenesis," *Brain, Behavior, and Immunity*, vol. 25, no. 2, pp. 181–213, 2011.

[5] G. Yang, C. N. Parkhurst, S. Hayes, and W.-B. Gan, "Peripheral elevation of TNF-α leads to early synaptic abnormalities in the mouse somatosensory cortex in experimental autoimmune encephalomyelitis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 25, pp. 10306–10311, 2013.

[6] D. J. MacEwan, "TNF receptor subtype signalling: differences and cellular consequences," *Cellular Signalling*, vol. 14, no. 6, pp. 477–492, 2002.

[7] M. Santello, P. Bezzi, and A. Volterra, "TNFα controls glutamatergic gliotransmission in the hippocampal dentate gyrus," *Neuron*, vol. 69, no. 5, pp. 988–1001, 2011.

[8] D. Stellwagen and R. C. Malenka, "Synaptic scaling mediated by glial TNF-α," *Nature*, vol. 440, no. 7087, pp. 1054–1059, 2006.

[9] E. C. Beattie, "Control of synaptic strength by glial TNFα," *Science*, vol. 295, no. 5563, pp. 2282–2285, 2002.

[10] C. A. Dinarello, "The IL-1 family and inflammatory diseases," *Clinical and Experimental Rheumatology*, vol. 20, 5 Suppl 27, pp. S1–13, 2002.

[11] M. Stampanoni Bassi, F. Mori, F. Buttari et al., "Neurophysiology of synaptic functioning in multiple sclerosis," *Clinical Neurophysiology*, vol. 128, no. 7, pp. 1148–1157, 2017.

[12] A. Citri and R. C. Malenka, "Synaptic plasticity: multiple forms, functions, and mechanisms," *Neuropsychopharmacology*, vol. 33, no. 1, pp. 18–41, 2008.

[13] R. A. Nicoll, "A brief history of long-term potentiation," *Neuron*, vol. 93, no. 2, pp. 281–290, 2017.

[14] C. Luscher and R. C. Malenka, "NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD)," *Cold Spring Harbor Perspectives in Biology*, vol. 4, no. 6, 2012.

[15] C. R. Bramham, P. F. Worley, M. J. Moore, and J. F. Guzowski, "The immediate early gene *arc/arg3.1*: regulation, mechanisms, and function," *The Journal of Neuroscience*, vol. 28, no. 46, pp. 11760–11767, 2008.

[16] J. R. Whitlock, A. J. Heynen, M. G. Shuler, and M. F. Bear, "Learning induces long-term potentiation in the hippocampus," *Science*, vol. 313, no. 5790, pp. 1093–1097, 2006.

[17] J. Kenney and D. Manahan-Vaughan, "Learning-facilitated synaptic plasticity occurs in the intermediate hippocampus in association with spatial learning," *Frontiers in Synaptic Neuroscience*, vol. 5, p. 10, 2013.

[18] E. Pastalkova, P. Serrano, D. Pinkhasova, E. Wallace, A. A. Fenton, and T. C. Sacktor, "Storage of spatial information by the maintenance mechanism of LTP," *Science*, vol. 313, no. 5790, pp. 1141–1144, 2006.

[19] R. Shema, T. C. Sacktor, and Y. Dudai, "Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKMζ," *Science*, vol. 317, no. 5840, pp. 951–953, 2007.

[20] P. Serrano, E. L. Friedman, J. Kenney et al., "PKMζ maintains spatial, instrumental, and classically conditioned long-term memories," *PLoS Biology*, vol. 6, no. 12, pp. 2698–2706, 2008.

[21] J.-I. Tanaka, Y. Horiike, M. Matsuzaki, T. Miyazaki, G. C. R. Ellis-Davies, and H. Kasai, "Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines," *Science*, vol. 319, no. 5870, pp. 1683–1687, 2008.

[22] Y. Liu, T. P. Wong, M. Aarts et al., "NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both *in vitro* and *in vivo*," *The Journal of Neuroscience*, vol. 27, no. 11, pp. 2846–2857, 2007.

[23] T. E. Bartlett and Y. T. Wang, "The intersections of NMDAR-dependent synaptic plasticity and cell survival," *Neuropharmacology*, vol. 74, pp. 59–68, 2013.

[24] B. Xu, W. Gottschalk, A. Chow et al., "The role of brain-derived neurotrophic factor receptors in the mature hippocampus: modulation of long-term potentiation through a presynaptic mechanism involving TrkB," *The Journal of Neuroscience*, vol. 20, no. 18, pp. 6888–6897, 2000.

[25] M. M. Poo, "Neurotrophins as synaptic modulators," *Nature Reviews Neuroscience*, vol. 2, no. 1, pp. 24–32, 2001.

[26] M. Kaneko, D. Stellwagen, R. C. Malenka, and M. P. Stryker, "Tumor necrosis factor-α mediates one component of competitive, experience-dependent plasticity in developing visual cortex," *Neuron*, vol. 58, no. 5, pp. 673–680, 2008.

[27] H. Schneider, F. Pitossi, D. Balschun, A. Wagner, A. del Rey, and H. O. Besedovsky, "A neuromodulatory role of interleukin-1β in the hippocampus," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 13, pp. 7778–7783, 1998.

[28] A. Avital, I. Goshen, A. Kamsler et al., "Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity," *Hippocampus*, vol. 13, no. 7, pp. 826–834, 2003.

[29] A. N. Coogan, L. A. O'Neill, and J. J. O'Connor, "The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1β on long-term potentiation in the rat dentate gyrus *in vitro*," *Neuroscience*, vol. 93, no. 1, pp. 57–69, 1999.

[30] A. W. Schmid, M. A. Lynch, and C. E. Herron, "The effects of IL-1 receptor antagonist on beta amyloid mediated depression of LTP in the rat CA1 in vivo," *Hippocampus*, vol. 19, no. 7, pp. 670–676, 2009.

[31] B. Viviani, S. Bartesaghi, F. Gardoni et al., "Interleukin-1β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases," *The Journal of Neuroscience*, vol. 23, no. 25, pp. 8692–8700, 2003.

[32] I. Goshen, T. Kreisel, H. Ounallah-Saad et al., "A dual role for interleukin-1 in hippocampal-dependent memory processes," *Psychoneuroendocrinology*, vol. 32, no. 8-10, pp. 1106–1115, 2007.

[33] G. G. Turrigiano, K. R. Leslie, N. S. Desai, L. C. Rutherford, and S. B. Nelson, "Activity-dependent scaling of quantal amplitude in neocortical neurons," *Nature*, vol. 391, no. 6670, pp. 892–896, 1998.

[34] G. G. Turrigiano, "The dialectic of Hebb and homeostasis," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 372, no. 1715, article 20160258, 2017.

[35] D. V. Lissin, S. N. Gomperts, R. C. Carroll et al., "Activity differentially regulates the surface expression of synaptic AMPA and NMDA glutamate receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 12, pp. 7097–7102, 1998.

[36] M. A. Gainey, J. R. Hurvitz-Wolff, M. E. Lambo, and G. G. Turrigiano, "Synaptic scaling requires the GluR2 subunit of the AMPA receptor," *The Journal of Neuroscience*, vol. 29, no. 20, pp. 6479–6489, 2009.

[37] J. D. Shepherd and R. L. Huganir, "The cell biology of synaptic plasticity: AMPA receptor trafficking," *Annual Review of Cell and Developmental Biology*, vol. 23, no. 1, pp. 613–643, 2007.

[38] A. V. Tzingounis and R. A. Nicoll, "Arc/Arg3.1: linking gene expression to synaptic plasticity and memory," *Neuron*, vol. 52, no. 3, pp. 403–407, 2006.

[39] J. D. Shepherd, G. Rumbaugh, J. Wu et al., "Arc/Arg3.1 mediates homeostatic synaptic scaling of AMPA receptors," *Neuron*, vol. 52, no. 3, pp. 475–484, 2006.

[40] O. Nikolaienko, S. Patil, M. S. Eriksen, and C. R. Bramham, "Arc protein: a flexible hub for synaptic plasticity and cognition," *Seminars in Cell & Developmental Biology*, vol. 77, pp. 33–42, 2018.

[41] N. S. Desai, R. H. Cudmore, S. B. Nelson, and G. G. Turrigiano, "Critical periods for experience-dependent synaptic scaling in visual cortex," *Nature Neuroscience*, vol. 5, no. 8, pp. 783–789, 2002.

[42] T. Keck, G. B. Keller, R. I. Jacobsen, U. T. Eysel, T. Bonhoeffer, and M. Hubener, "Synaptic scaling and homeostatic plasticity in the mouse visual cortex in vivo," *Neuron*, vol. 80, no. 2, pp. 327–334, 2013.

[43] K. B. Hengen, A. Torrado Pacheco, J. N. McGregor, S. D. Van Hooser, and G. G. Turrigiano, "Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake," *Cell*, vol. 165, no. 1, pp. 180–191, 2016.

[44] H. Pribiag and D. Stellwagen, "TNF-α downregulates inhibitory neurotransmission through protein phosphatase 1-dependent trafficking of $GABA_A$ receptors," *The Journal of Neuroscience*, vol. 33, no. 40, pp. 15879–15893, 2013.

[45] M. Santello and A. Volterra, "TNFα in synaptic function: switching gears," *Trends in Neurosciences*, vol. 35, no. 10, pp. 638–647, 2012.

[46] D. Stellwagen, E. C. Beattie, J. Y. Seo, and R. C. Malenka, "Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-α," *The Journal of Neuroscience*, vol. 25, no. 12, pp. 3219–3228, 2005.

[47] S. J. Barnes, E. Franzoni, R. I. Jacobsen et al., "Deprivation-induced homeostatic spine scaling *in vivo* is localized to dendritic branches that have undergone recent spine loss," *Neuron*, vol. 96, no. 4, pp. 871–882.e5, 2017.

[48] G. M. Lewitus, H. Pribiag, R. Duseja, M. St-Hilaire, and D. Stellwagen, "An adaptive role of TNFα in the regulation of striatal synapses," *The Journal of Neuroscience*, vol. 34, no. 18, pp. 6146–6155, 2014.

[49] A. Ranson, C. E. J. Cheetham, K. Fox, and F. Sengpiel, "Homeostatic plasticity mechanisms are required for juvenile, but not adult, ocular dominance plasticity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 4, pp. 1311–1316, 2012.

[50] H. Kettenmann, F. Kirchhoff, and A. Verkhratsky, "Microglia: new roles for the synaptic stripper," *Neuron*, vol. 77, no. 1, pp. 10–18, 2013.

[51] Y. Wu, L. Dissing-Olesen, B. A. MacVicar, and B. Stevens, "Microglia: dynamic mediators of synapse development and plasticity," *Trends in Immunology*, vol. 36, no. 10, pp. 605–613, 2015.

[52] U.-K. Hanisch and H. Kettenmann, "Microglia: active sensor and versatile effector cells in the normal and pathologic brain," *Nature Neuroscience*, vol. 10, no. 11, pp. 1387–1394, 2007.

[53] D. Becker, N. Zahn, T. Deller, and A. Vlachos, "Tumor necrosis factor alpha maintains denervation-induced homeostatic synaptic plasticity of mouse dentate granule cells," *Frontiers in Cellular Neuroscience*, vol. 7, p. 257, 2013.

[54] D. Becker, T. Deller, and A. Vlachos, "Tumor necrosis factor (TNF)-receptor 1 and 2 mediate homeostatic synaptic plasticity of denervated mouse dentate granule cells," *Scientific Reports*, vol. 5, no. 1, article 12726, 2015.

[55] Y. Liu, L.-J. Zhou, J. Wang et al., "TNF-α differentially regulates synaptic plasticity in the hippocampus and spinal cord by microglia-dependent mechanisms after peripheral nerve injury," *The Journal of Neuroscience*, vol. 37, no. 4, pp. 871–881, 2017.

[56] W.-J. Ren, Y. Liu, L.-J. Zhou et al., "Peripheral nerve injury leads to working memory deficits and dysfunction of the hippocampus by upregulation of TNF-α in rodents," *Neuropsychopharmacology*, vol. 36, no. 5, pp. 979–992, 2011.

[57] V. Tancredi, G. D'Arcangelo, F. Grassi et al., "Tumor necrosis factor alters synaptic transmission in rat hippocampal slices," *Neuroscience Letters*, vol. 146, no. 2, pp. 176–178, 1992.

[58] A. J. Cunningham, C. A. Murray, L. A. O'Neill, M. A. Lynch, and J. J. O'Connor, "Interleukin-1β (IL-1β) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro," *Neuroscience Letters*, vol. 203, no. 1, pp. 17–20, 1996.

[59] A. M. Wall, G. Mukandala, N. H. Greig, and J. J. O'Connor, "Tumor necrosis factor-alpha potentiates long-term potentiation in the rat dentate gyrus after acute hypoxia," *Journal of Neuroscience Research*, vol. 93, no. 5, pp. 815–829, 2015.

[60] L. C. Pettigrew, R. J. Kryscio, and C. M. Norris, "The TNFα-transgenic rat: hippocampal synaptic integrity, cognition, function, and post-ischemic cell loss," *PLoS One*, vol. 11, no. 5, article e0154721, p. 11, 2016.

[61] F. P. Bellinger, S. Madamba, and G. R. Siggins, "Interleukin 1β inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus," *Brain Research*, vol. 628, no. 1-2, pp. 227–234, 1993.

[62] H. Katsuki, S. Nakai, Y. Hirai, K. Akaji, Y. Kiso, and M. Satoh, "Interleukin-1β inhibits long-term potentiation in the CA3 region of mouse hippocampal slices," *European Journal of Pharmacology*, vol. 181, no. 3, pp. 323–326, 1990.

[63] E. Vereker, E. O'Donnell, and M. A. Lynch, "The inhibitory effect of interleukin-1β on long-term potentiation is coupled with increased activity of stress-activated protein kinases," *The Journal of Neuroscience*, vol. 20, no. 18, pp. 6811–6819, 2000.

[64] L. Tong, G. A. Prieto, E. A. Kramar et al., "Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1β via p38 mitogen-activated protein kinase," *The Journal of Neuroscience*, vol. 32, no. 49, pp. 17714–17724, 2012.

[65] C. A. Murray and M. A. Lynch, "Evidence that increased hippocampal expression of the cytokine interleukin-1β is a common trigger for age- and stress-induced impairments in long-term potentiation," *The Journal of Neuroscience*, vol. 18, no. 8, pp. 2974–2981, 1998.

[66] T. Han, Y. Qin, C. Mou, M. Wang, M. Jiang, and B. Liu, "Seizure induced synaptic plasticity alteration in hippocampus is mediated by IL-1β receptor through PI3K/Akt pathway," *American Journal of Translational Research*, vol. 8, no. 10, pp. 4499–4509, 2016.

[67] Y. Imamura, H. Wang, N. Matsumoto et al., "Interleukin-1β causes long-term potentiation deficiency in a mouse model of

septic encephalopathy," *Neuroscience*, vol. 187, pp. 63–69, 2011.

[68] J. R. Erion, M. Wosiski-Kuhn, A. Dey et al., "Obesity elicits interleukin 1-mediated deficits in hippocampal synaptic plasticity," *The Journal of Neuroscience*, vol. 34, no. 7, pp. 2618–2631, 2014.

[69] W. Swardfager, K. Lanctot, L. Rothenburg, A. Wong, J. Cappell, and N. Herrmann, "A meta-analysis of cytokines in Alzheimer's disease," *Biological Psychiatry*, vol. 68, no. 10, pp. 930–941, 2010.

[70] R. M. Barrientos, M. M. Kitt, L. R. Watkins, and S. F. Maier, "Neuroinflammation in the normal aging hippocampus," *Neuroscience*, vol. 309, pp. 84–99, 2015.

[71] A. Gentile, F. Mori, S. Bernardini, and D. Centonze, "Role of amyloid-β CSF levels in cognitive deficit in MS," *Clinica Chimica Acta*, vol. 449, pp. 23–30, 2015.

[72] S. Tu, S. Okamoto, S. A. Lipton, and H. Xu, "Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease," *Molecular Neurodegeneration*, vol. 9, no. 1, p. 48, 2014.

[73] K. P. MacPherson, P. Sompol, G. T. Kannarkat et al., "Peripheral administration of the soluble TNF inhibitor XPro1595 modifies brain immune cell profiles, decreases beta-amyloid plaque load, and rescues impaired long-term potentiation in 5xFAD mice," *Neurobiology of Disease*, vol. 102, pp. 81–95, 2017.

[74] A. M. Minogue, A. W. Schmid, M. P. Fogarty et al., "Activation of the c-Jun N-terminal kinase signaling cascade mediates the effect of amyloid-β on long term potentiation and cell death in hippocampus: a role for interleukin-1β?," *Journal of Biological Chemistry*, vol. 278, no. 30, pp. 27971–27980, 2003.

[75] Q. Wang, J. Wu, M. J. Rowan, and R. Anwyl, "β-amyloid inhibition of long-term potentiation is mediated via tumor necrosis factor," *European Journal of Neuroscience*, vol. 22, no. 11, pp. 2827–2832, 2005.

[76] G. Wang, J. Gilbert, and H.-Y. Man, "AMPA receptor trafficking in homeostatic synaptic plasticity: functional molecules and signaling cascades," *Neural Plasticity*, vol. 2012, Article ID 825364, 12 pages, 2012.

[77] A. Musella, G. Mandolesi, F. Mori, A. Gentile, and D. Centonze, "Linking synaptopathy and gray matter damage in multiple sclerosis," *Multiple Sclerosis Journal*, vol. 22, no. 2, pp. 146–149, 2016.

[78] M. Calabrese, R. Magliozzi, O. Ciccarelli, J. J. G. Geurts, R. Reynolds, and R. Martin, "Exploring the origins of grey matter damage in multiple sclerosis," *Nature Reviews Neuroscience*, vol. 16, no. 3, pp. 147–158, 2015.

[79] G. Mandolesi, A. Gentile, A. Musella et al., "Synaptopathy connects inflammation and neurodegeneration in multiple sclerosis," *Nature Reviews Neurology*, vol. 11, no. 12, pp. 711–724, 2015.

[80] A. Gentile, D. Fresegna, M. Federici et al., "Dopaminergic dysfunction is associated with IL-1β-dependent mood alterations in experimental autoimmune encephalomyelitis," *Neurobiology of Disease*, vol. 74, pp. 347–358, 2015.

[81] S. Weiss, F. Mori, S. Rossi, and D. Centonze, "Disability in multiple sclerosis: when synaptic long-term potentiation fails," *Neuroscience & Biobehavioral Reviews*, vol. 43, pp. 88–99, 2014.

[82] F. Mori, R. Nistico, G. Mandolesi et al., "Interleukin-1β promotes long-term potentiation in patients with multiple sclerosis," *NeuroMolecular Medicine*, vol. 16, no. 1, pp. 38–51, 2014.

[83] S. Rossi, C. Motta, V. Studer et al., "Tumor necrosis factor is elevated in progressive multiple sclerosis and causes excitotoxic neurodegeneration," *Multiple Sclerosis Journal*, vol. 20, no. 3, pp. 304–312, 2013.

[84] G. Mandolesi, A. Gentile, A. Musella, and D. Centonze, "Il-1β dependent cerebellar synaptopathy in a mouse mode of multiple sclerosis," *The Cerebellum*, vol. 14, no. 1, pp. 19–22, 2015.

[85] D. Centonze, L. Muzio, S. Rossi et al., "Inflammation triggers synaptic alteration and degeneration in experimental autoimmune encephalomyelitis," *The Journal of Neuroscience*, vol. 29, no. 11, pp. 3442–3452, 2009.

[86] N. Haji, G. Mandolesi, A. Gentile et al., "TNF-α-mediated anxiety in a mouse model of multiple sclerosis," *Experimental Neurology*, vol. 237, no. 2, pp. 296–303, 2012.

[87] S. Chowdhury, J. D. Shepherd, H. Okuno et al., "Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking," *Neuron*, vol. 52, no. 3, pp. 445–459, 2006.

[88] A. R. Ferguson, R. N. Christensen, J. C. Gensel et al., "Cell death after spinal cord injury is exacerbated by rapid TNFα-induced trafficking of GluR2-lacking AMPARs to the plasma membrane," *The Journal of Neuroscience*, vol. 28, no. 44, pp. 11391–11400, 2008.

[89] D. Leonoudakis, P. Zhao, and E. C. Beattie, "Rapid tumor necrosis factor α-induced exocytosis of glutamate receptor 2-lacking AMPA receptors to extrasynaptic plasma membrane potentiates excitotoxicity," *The Journal of Neuroscience*, vol. 28, no. 9, pp. 2119–2130, 2008.

[90] S. Rossi, L. Muzio, V. De Chiara et al., "Impaired striatal GABA transmission in experimental autoimmune encephalomyelitis," *Brain, Behavior, and Immunity*, vol. 25, no. 5, pp. 947–956, 2011.

[91] S. Habbas, M. Santello, D. Becker et al., "Neuroinflammatory TNFα impairs memory via astrocyte signaling," *Cell*, vol. 163, no. 7, pp. 1730–1741, 2015.

[92] R. Nistico, D. Mango, G. Mandolesi et al., "Inflammation subverts hippocampal synaptic plasticity in experimental multiple sclerosis," *PLoS One*, vol. 8, no. 1, article e54666, 2013.

[93] G. Mandolesi, A. Musella, A. Gentile et al., "Interleukin-1β alters glutamate transmission at Purkinje cell synapses in a mouse model of multiple sclerosis," *The Journal of Neuroscience*, vol. 33, no. 29, pp. 12105–12121, 2013.

[94] M. Di Filippo, D. Chiasserini, F. Gardoni et al., "Effects of central and peripheral inflammation on hippocampal synaptic plasticity," *Neurobiology of Disease*, vol. 52, pp. 229–236, 2013.

[95] M. Di Filippo, A. de Iure, C. Giampa et al., "Persistent activation of microglia and NADPH oxidase drive hippocampal dysfunction in experimental multiple sclerosis," *Scientific Reports*, vol. 6, no. 1, article 20926, 2016.

[96] N. Prochnow, R. Gold, and A. Haghikia, "An electrophysiologic approach to quantify impaired synaptic transmission and plasticity in experimental autoimmune encephalomyelitis," *Journal of Neuroimmunology*, vol. 264, no. 1-2, pp. 48–53, 2013.

[97] D. Y. Kim, J. Hao, R. Liu, G. Turner, F.-D. Shi, and J. M. Rho, "Inflammation-mediated memory dysfunction and effects of

a ketogenic diet in a murine model of multiple sclerosis," *PLoS One*, vol. 7, no. 5, article e35476, 2012.

[98] T. Novkovic, O. Shchyglo, R. Gold, and D. Manahan-Vaughan, "Hippocampal function is compromised in an animal model of multiple sclerosis," *Neuroscience*, vol. 309, pp. 100–112, 2015.

[99] G. Mosayebi, M. R. Soleyman, M. Khalili, M. Mosleh, and M. R. Palizvan, "Changes in synaptic transmission and long-term potentiation induction as a possible mechanism for learning disability in an animal model of multiple sclerosis," *International Neurourology Journal*, vol. 20, no. 1, pp. 26–32, 2016.

[100] V. Planche, A. Panatier, B. Hiba et al., "Selective dentate gyrus disruption causes memory impairment at the early stage of experimental multiple sclerosis," *Brain, Behavior, and Immunity*, vol. 60, pp. 240–254, 2017.

[101] M. Di Filippo, A. de Iure, V. Durante et al., "Synaptic plasticity and experimental autoimmune encephalomyelitis: implications for multiple sclerosis," *Brain Research*, vol. 1621, pp. 205–213, 2015.

Hindawi
Neural Plasticity
Volume 2018, Article ID 1824713, 15 pages
https://doi.org/10.1155/2018/1824713

Review Article

Roles of Gasotransmitters in Synaptic Plasticity and Neuropsychiatric Conditions

Ulfuara Shefa,[1] Dokyoung Kim,[1,2] Min-Sik Kim,[3] Na Young Jeong,[4] and Junyang Jung[1,2,5]

[1]*Department of Biomedical Science, Graduate School, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea*
[2]*Department of Anatomy and Neurobiology, College of Medicine, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea*
[3]*Department of Applied Chemistry, College of Applied Science, Kyung Hee University, Deogyeong-daero, Giheung-gu, Yongin-si, Gyeonggi-do 17104, Republic of Korea*
[4]*Department of Anatomy and Cell Biology, College of Medicine, Dong-A University, 32 Daesingongwon-ro, Seo-gu, Busan 49201, Republic of Korea*
[5]*East-West Medical Research Institute, Kyung Hee University, 26 Kyungheedae-ro, Dongdaemun-gu, 13 Seoul 02447, Republic of Korea*

Correspondence should be addressed to Junyang Jung; jjung@khu.ac.kr

Received 4 January 2018; Revised 25 February 2018; Accepted 11 March 2018; Published 6 May 2018

Academic Editor: Steven W. Johnson

Synaptic plasticity is important for maintaining normal neuronal activity and proper neuronal functioning in the nervous system. It is crucial for regulating synaptic transmission or electrical signal transduction to neuronal networks, for sharing essential information among neurons, and for maintaining homeostasis in the body. Moreover, changes in synaptic or neural plasticity are associated with many neuropsychiatric conditions, such as schizophrenia (SCZ), bipolar disorder (BP), major depressive disorder (MDD), and Alzheimer's disease (AD). The improper maintenance of neural plasticity causes incorrect neurotransmitter transmission, which can also cause neuropsychiatric conditions. Gas neurotransmitters (gasotransmitters), such as hydrogen sulfide (H_2S), nitric oxide (NO), and carbon monoxide (CO), play roles in maintaining synaptic plasticity and in helping to restore such plasticity in the neuronal architecture in the central nervous system (CNS). Indeed, the upregulation or downregulation of these gasotransmitters may cause neuropsychiatric conditions, and their amelioration may restore synaptic plasticity and proper neuronal functioning and thereby improve such conditions. Understanding the specific molecular mechanisms underpinning these effects can help identify ways to treat these neuropsychiatric conditions.

1. Introduction

The polish psychologist Konorski (1948) first used the term "synaptic plasticity" to describe consistent and activity-dependent changes in synaptic strength [1]. Synaptic plasticity is an experience-dependent change in synaptic strength [2]. Changes in synaptic strength are essential for information storage during memory formation [3], and recent work has revealed that synaptic plasticity also plays roles in other adaptive responses, including mood stability, drug addiction, and chronic pain [4]. The mechanisms underpinning synaptic plasticity are broadly linked to long-term memory. Synapse modifications are commonly monitored by two important phenomena: long-term potentiation (LTP) and long-term depression (LTD), which cause an increase or a reduction in synaptic strength, respectively. LTP and LTD also have roles in memory and learning [1]. Neurotransmitters are the chemical messengers that activate, amplify, and harmonize signals between neurons and other cells in the body. Neuronal functions rely on a balance between the number of relevant excitatory and inhibitory processes, which may happen individually or concomitantly [5].

The gas neurotransmitters (gasotransmitters) in our body include hydrogen sulfide (H_2S), nitric oxide (NO), and carbon monoxide (CO); they play essential roles in normal physiology and under pathological conditions. H_2S is a member of the gasotransmitter family that is associated with the maintenance of neuronal plasticity, excitability, and the central nervous system (CNS) [6]. *N*-Methyl-D-aspartate (NMDA) receptors are targets of H_2S in the brain; H_2S potentiates the activity of NMDA receptors and facilitates the induction of hippocampal LTP [7]. Hence, a recent study demonstrated that H_2S could reduce NMDA receptor-mediated currents in pyramidal neurons of the Cornu Ammonis (CA3) region of neonatal hippocampal slices [6]. NO is a ubiquitous signaling molecule in the brain as well as in other organs in the body, and many reviews have described its role in retrograde signaling [8], cellular function, synaptic plasticity [9], development, excitotoxicity, blood flow, and mental health [10]. NO inhibits the activity of NMDA receptors and thereby reduces the effects of glutamate and induces changes in neural transmission. A reduction in NMDA receptor (NMDAR) expression is associated with the change in synaptic plasticity driven by the age-related conditions in sensory input, demonstrating age-related impairment in the function of the NMDAR/NO signaling pathway in the CNS [11]. Physiologically, CO is generated by two heme oxygenases, hemeoxygenase-1 (HO-1) and hemeoxygenase-2 (HO-2), which catalyze the catabolism of heme groups [12]. HO-2 is concentrated in hippocampal pyramidal cells; therefore, CO might be a candidate retrograde messenger for LTP as the HO inhibitor zinc protoporphyrin IX (Znpp-9) blocks the induction of LTP in hippocampal slices [13].

In this review, we will briefly describe the role of synaptic plasticity in normal neuronal functioning or homeostasis and examine how alterations in neural plasticity hamper the release and signaling of neurotransmitters, such as H_2S, NO, and CO, to cause neuropsychiatric conditions, such as major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD), and Alzheimer's disease (AD). We will also address how the upregulation or downregulation of these gasotransmitters affects disease progression. Finally, we will discuss therapeutic options and how, by understanding the pathways through which alterations in neural plasticity cause disorders, we can target the responsible molecules to prevent these neuropsychiatric conditions.

2. Synaptic Plasticity and Its Neurobiology

Synaptic plasticity in the mature nervous system includes structural and morphological modifications, such as dendritic spine growth and synaptogenesis [14]. These modifications are the cellular response to the changes in neuronal activity that are thought to be responsible for learning and memory [15]. The mitochondria present in axonal terminals and the dendrites of neurons play important roles in synaptic activity [16].

Various neurotransmitter receptors are functionally linked with protein kinases as well as other G-proteins that modulate cascades of molecules which in turn maintain essential cellular functions [17]. As an example, the mitogen-activated protein kinase- (MAPK-) related pathway activates transcription factors associated with learning, memory, and cell proliferation as well as apoptosis. This pathway intricates extracellular stimuli via the phosphorylation of c-Jun *N*-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and P38 as well as other kinases. Similarly, the MAPK-involved pathway and $3'$-$5'$-cyclic adenosine monophosphate- (cAMP-) associated pathway are also jointed to activate neurotransmitter receptors as well as modulate cellular functions via the activation of protein kinase A (PKA), exchange protein stimulated by cAMP (EPAC), and other molecules [18]. Modifications of the MAPK-and c-AMP-related signaling pathways may affect intracellular Ca^{2+} levels, neurotransmitter receptors, transcription factors, and the cross link between signaling pathways as well as other biological functions which is essential for neuroplasticity [19].

Structurally, synaptic plasticity involves the insertion into or the removal of α-amino-3-hydroxy-5-methyl-isoxazole-4-propanoic acid (AMPA) receptors from the postsynaptic membrane and the enlargement or shrinkage of the dendritic spines where most excitatory synapses (~90%) are located [20]. Functionally, synaptic plasticity is regarded as the LTP or LTD of synaptic strength, demonstrating changes in conductance via AMPA receptors (AMPARs) in the postsynaptic membrane. During the period of plasticity, NMDAR activation allows calcium ions (Ca^{2+}) to cross the postsynaptic membrane and initiate intracellular signaling cascades (Figure 1). These cascades trigger gene transcription, AMPAR trafficking via action dynamics, reorganization of the cytoskeleton, and enlargement or elimination of dendritic spines. The integrity of the synaptic structure, AMPAR trafficking, and dendritic spine dynamics are all pivotal for generating lasting synaptic plasticity changes (Figure 1) [20].

On the neurobiological level, learning and memory depend on regulated signaling processes at synapses as well as synaptic communication between neurons and other cellular partners. Molecular-level plasticity can be driven by increased expression of plasticity-related genes, such as brain-derived neurotrophic factor (BDNF), calcium/calmodulin kinase II (CaMKII), and cyclic AMP (cAMP) response element binding (CREB) protein, as well as by enhanced surface expression of glutamatergic AMPARs and NMDARs. The neurotrophin BDNF and its signaling partners are the main regulators of synaptic plasticity, a biological process that regulates synaptic strength via neuronal activity [21]. Different neuromodulatory factors affect neuronal plasticity such as BDNF which may serve as a real mediator rather than simply a modulator of synaptic plasticity and synaptic communication [21]. Moreover, BDNF and neurotransmitter signaling cascades can work together in close temporal association to induce immediate and guided effects on synaptic plasticity [22]. However, more attention has been given to BDNF because specifically interfering with BDNF-related signaling is a key strategy for initiating neuronal and functionally restorative treatments for neurological and psychiatric disorders [23].

AMPARs and NMDARs are the receptors that synergize at postsynaptic terminals to facilitate different forms

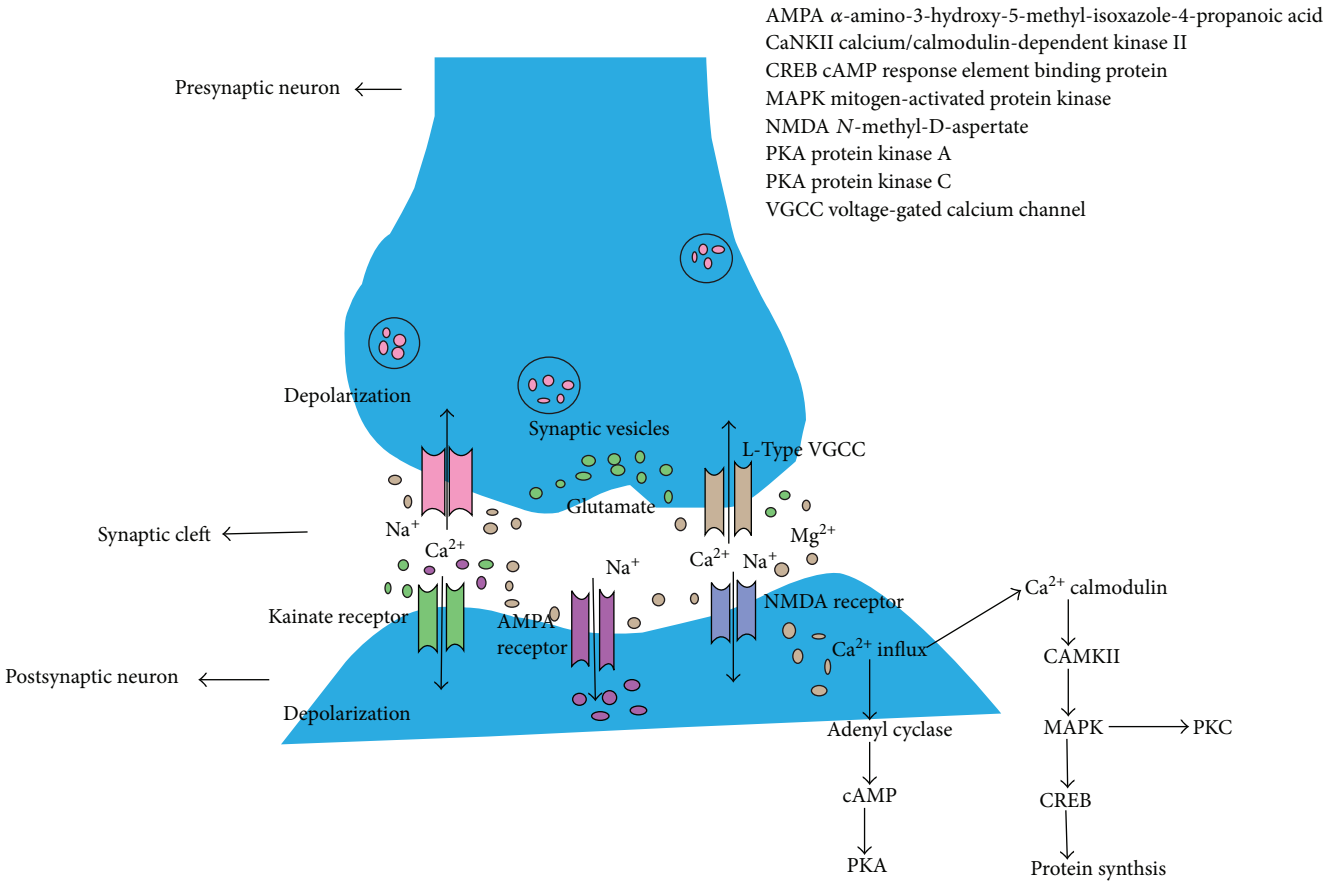


Figure 1: Transmission of signals through the synaptic junctions. Signals or impulses at the presynaptic terminal trigger the release of glutamate that binds to glutamate receptors at the postsynaptic membrane. Activation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propanoic acid (AMPA) as well as kainate receptors which subsequently transport sodium ions that trigger postsynaptic depolarization. As membrane potential changes, it initiates the release of magnesium ions which blocks *N*-methyl-D-aspartate (NMDA) receptors. Influx of calcium via NMDA channels sets off a chain of events which establish long-term potentiation. Kainate receptors at the presynaptic end also seem to facilitate synaptic transmission at particular synapses by accumulating neurotransmitter release.

of synaptic plasticity (Figure 1). Constant activation of AMPARs by a series of impulses arriving at presynaptic terminals leads to depolarization of the presynaptic membrane, which removes the magnesium ions (Mg^{2+}) that are obstructed at NMDARs [24]. Hence, consistent with the Hebb hypothesis, the simultaneous excitation of pre- and postsynaptic neurons expedites the gating of NMDA channels and strengthens the synapse. This is a crucial feature of NMDA channels that is specifically associated with synaptic plasticity and its high permeability to calcium. Consequently, the second messenger calcium modulates a battery of signaling pathways and the responses that collectively elicit synaptic modification [25]. NMDARs are also involved in synaptic plasticity, but the situation is far more complex, as many forms of LTP are imparted by diverse inputs in various neurons. One intriguing case is that of activity-dependent synaptic plasticity, which is stimulated by presynaptic NMDA channels. In the lateral nucleus of the amygdala, neuronal activity induces a form of LTP that requires NMDARs but is independent of postsynaptic activity [26]. These observations suggest that NMDA functions, which are critical for learning and memory, are not limited to postsynaptic terminals [25].

Voltage-gated calcium channels (VGCCs) play roles in signal transduction between neurons as well as in various forms of synaptic plasticity. Interestingly, patients with AD express higher levels of L-type VGCC in the hippocampus compared with control subjects [27]. Activity-dependent neuroplastic mechanisms in the hippocampus that are fundamental to learning and memory, such as LTP, can be altered by the preceding synaptic activity. The concept of neuroplasticity has been implicated in various neurological and psychiatric diseases and conditions, including AD, depression, SCZ, aging, epilepsy, neurodevelopmental disorders, metabolic disorders, and neuroinflammation, such as multiple sclerosis (MS) [28].

In summary, various receptors and ion channels regulate synaptic plasticity, proper neural functioning, and neural homeostasis.

3. Gasotransmitters (H_2S, NO, and CO) in the Nervous System

Three main gasotransmitters that play crucial physiological roles in the body were discovered recently: H_2S,

CO, and NO. These gasotransmitters also have pathologic functions [29].

3.1. H_2S. H_2S is an essential signaling molecule with many homeostatic functions, such as neurotransmission and neuromodulation; it is also associated with learning, memory, and nociception [29]. *In vivo*, five enzymes are associated with H_2S synthesis: cystathionine β-synthase (CBS), 3-mercaptopyruvate sulfurtransferase (3-MST), cystathionine γ-lyase (CSE), cysteine aminotransferase (CAT), and D-amino acid oxidase (DAAO) [30]. CBS is thought to be the major H_2S-producing enzyme in the brain [31].

Novel signaling molecules linked to polysulfide (H_2S_n) such as hydrogen persulfide and trisulfide (H_2S_2 and H_2S_3) help maintain neuronal transmission, vascular tone, cytoprotection, inflammation, and oxygen-sensing. A recent study reported that H_2S_2, H_2S_3, and H_2S are generated by 3-MST [32]. H_2S_2 and H_2S_3 are also produced via an interaction between H_2S and NO. H_2S_n performs additional physiological functions, such as stimulating transient receptor potential ankyrin 1 (TRPA1) channels to impart Ca^{2+} influx in astrocytes [33, 34] and dorsal root ganglion (DRG) neurons [35]. Additionally, H_2S_2 along with H_2S_3 shields neuronal cells from oxidative as well as carbonyl stresses through exerting reduced synthesis of glutathione, which is dependent on the nuclear factor erythroid 2-related factor 2 (Nrf2) [36]. Hylin and Wood demonstrated that cysteine residues in proteins can be persulfurated in the presence of 3-mercaptopyruvate (3-MP), a substrate of 3-MST [37]. Another potential mechanism of persulfuration involves H_2S_2 and H_2S_3 generated by 3-MST, which promptly interact with free cysteine and glutathione (GSH) to generate cysteine-persulfide (Cys-SSH) and glutathione-persulfide (GSSH) and also react with the cysteine residues in proteins to produce persulfurated proteins. Alternatively, 3-MST can transfer sulfur from 3-MP to cysteine, GSH, H_2S, and cysteine residues to generate Cys-SSH, GSSH, H_2S_2, and persulfurated proteins. It is possible that these pathways proceed together to generate persulfurated species [38].

H_2S accelerates the initiation of hippocampal LTP, which is a synaptic model of memory development, by increasing the function of NMDARs [7]. CBS is expressed in the brain, and the neuronal activity of H_2S stimulates the flow of Ca^{2+} between astrocytes and neurons to adjust synaptic function [39]. The responses of astrocytes to H_2S are suppressed by wide-spectrum transient receptor potential (TRP) channel blockers, lanthanide ions (La^{3+}), gadolinium ion (Gd^{3+}), and ruthenium red (RR). In a 2013 study, Kimura et al. showed that polysulfide induces Ca^{2+} inflow by stimulating transitory receptor potential TRPA1 channels in rat astrocytes [33]. The optimum activity was imparted at 0.5 μM, which is 1/130 of the concentration of H_2S needed to obtain feedback of similar magnitude. Additionally, TRPA1-specific agonists, allyl isothiocyanate, and cinnamaldehyde induced Ca^{2+} inflow, whereas responses to polysulfides were suppressed by the TRAP1-specific inhibitors HC-030031 and AP-18 as well as by TRAP1-specific small interfering RNA (siRNA). This study demonstrated that polysulfides are required for the H_2S-derived signaling molecules that activate TRP channels in the brain [33].

Kimura demonstrated that exogenous H_2S expedites the induction of hippocampal LTP by increasing NMDAR activity [40]. For example, an H_2S donor enhanced NMDAR-mediated currents in the entorhinal cortex and the potentiating effect of exogenous H_2S on NMDAR-dependent LTP has been revealed that physiological role of endogenous sulfhydration in plasticity [41]. Another recent study identified a crucial role for activity-dependent sulfhydration in D-serine-dependent synaptic plasticity. Specifically, neuronal activity facilitated H_2S production and sulfhydrated serine racemase (SR) formation, and use of an H_2S donor enhanced hippocampal D-serine availability, expedited hippocampal LTP via a D-serine-dependent pathway, and slowed age-related LTP impairment [41]. In this study, H_2S levels and SR sulfhydration were reduced significantly in aged rats. As H_2S is an important reducing agent, these changes restored D-serine levels in the hippocampus of aged rats and replenished the deficits in D-serine-dependent plasticity. Additionally, endogenous H_2S signals protected against the age-associated impairment of synaptic plasticity [41]. The results of this study suggest that H_2S-linked sulfhydration plays an essential role in D-serine-dependent synaptic plasticity, probably by regulating SR activation. Therefore, therapies that involve inhaled H_2S or compounds that moderately raise brain H_2S levels may be effective for the treatment of age-associated memory impairment [41].

3.2. NO. NO is regarded as a chemical transmitter which has essential functions in the mammalian central as well as peripheral nervous system [42]. NO is a gaseous molecule that can passively cross cell membranes via diffusion. It is generated by the conversion of the amino acid L-arginine into L-citrulline via the enzyme NO synthase (NOS) and inducible NOS (iNOS). Constitutive nitric oxide synthase (cNOS), or type I, is the neuronal NOS (nNOS), and it is expressed at high levels in the brain, especially in the cortex [43]. Additionally, type III or endothelial NOS (eNOS) is expressed in the endothelium. cNOS generates low levels of NO (nM range) for a short duration (seconds–minutes) under regular physiological conditions because it needs to bind to calmodulin, which occurs only while local calcium levels are increased [43].

NO is the second mediator that can activate NMDARs, which are a subtype of glutamatergic receptors [44]. NMDARs are related to the NO system. NMDAR activation persistently enhances the activity of neuronal nitric oxide synthase (nNOS) in the neuronal cytoplasm. It then catalyzes the generation of endogenous NO from L-arginine followed by the enhanced release of NO from neurons [45, 46]. Activation of these receptors by glutamate stimulates the calcium influx into cells and the generation of NO by NOS, which rapidly stimulates guanylate cyclase and increases cyclic guanosine monophosphate (cGMP) synthesis [47]. The concentration of NO reflects glutamatergic neurotransmission [48]. Hence, other glutamate receptors, such as AMPA, can also produce NO; this pathway modulates the release of glutamate and dopamine. AMPARs are important ion channels

that have four subunits that operate like NMDARs, such as Glu1–4 or GluA-D [49]. Nevertheless, AMPAR trafficking, expression, and S-nitrosylation activity are maintained by NO. An ATPase named *N*-ethylmaleimide-sensitive factor (NSF) is enriched in neurons which binds with GluR2, stabilizing or recycling AMPARs with postsynaptic membranes [50]. Physiologically, synaptic NSF is S-nitrosylated by endogenous, neuronally derived NO in the mouse brain. Activation of NMDAR increases the binding of NSF to GluR2, as well as the surface insertion of GluR2. Together, these studies revealed a NO-sensitive pathway involving NMDARs and AMPARs. In particular, NMDARs stimulate NO generation, which enhances NSF S-nitrosylation, stimulates its association with GluR2, and increases the surface expression of GluR2-containing AMPARs. However, the direct S-nitrosylation activity of AMPARs has not been studied [50]. Additionally, NO is associated with the storage, uptake, and release of mediators, such as acetylcholine, noradrenaline, gamma amino butyric acid (GABA), taurine, and a glycine [51]. NO can stimulate its own extrasynaptic receptors, which are located some distance from sites of NO synthesis. In addition, NO is associated with the process of development of the nervous system [8]. For example, nNOS-containing neurons actively participate in the rostral path of neuroblast migration, which involves new synaptic connections and influences neurogenesis [52]. Astrocyte migration is also regulated by the release of NO under the actions of iNOS. NO is also recognized as critical for the formation of synapses and the growth of nerve fibers [53].

3.3. CO. CO is a new gaseous neuromodulatory agent that functions as a neurotransmitter or neuromodulator [54]. CO is produced during heme metabolism by HO-1 and HO-2; HO-1 is an inducible enzyme, and HO-2 is constitutively expressed. HO is the enzyme responsible for CO synthesis *in vivo*; it catalyzes the metabolism of heme to biliverdin, free iron, and CO [55]. There are three distinct HO isoforms: HO-1, HO-2, and HO-3. Of these, HO-1 and HO-2 are the most studied and best known [56] and are expressed in many tissues, including neural tissue [57]. The CO generated from heme by HO stimulates soluble guanylate cyclase activity, which promotes an increase in cGMP in neurons as well as cardiovascular functions [58]. CO may also have involved in biological activities via alternative pathways, such as the activation of cyclooxygenase, which participates in fever generation by acting on the CNS [54]. In the CNS, the CO/heme oxygenase axis plays a vital role in processes associated with cytoprotection, vasomodulation, neuroinflammation, cell death, metabolism, and cellular redox responses [59]. CO was first recognized as a neurotransmitter by Verma et al. [60]. Their research led to broad investigations into CO, heme oxygenase, and the exogenous administration of CO as a method of imparting neuroprotection and regulating tissue homeostasis in response to pathophysiological conditions, such as cerebral ischemia, cerebrovasodilation, and neurodegenerative diseases [61]. In neurons, CO-induced cGMP generation helps protect from cell death, and NO signaling is associated with the anti-inflammatory effects of CO in microglia [62].

Semiquantitative cytokine profiling of cell lysates and conditioned culture medium demonstrated increased vascular endothelial growth factor (VEGF) levels in CO-treated cultures (cell lysates) compared with controls. This is consistent with other experiments describing that CO increases VEGF levels in astrocytes and cardiomyocytes [63]. Surprisingly, a decrease in neurotrophin-3 and an increase in neurotrophin-4 levels were found in lysates from cells treated with CO. Although no studies have assessed the effects of CO treatment on neurotrophin-3 and neurotrophin-4, both neurotrophins are associated with neuronal growth and synapse formation, maturation, and plasticity. Additionally, neurotrophin-3 is expressed in neural stem cells (NSCs), and it stimulates neuronal differentiation and survival [62].

In conclusion, various gasotransmitters, such as H_2S, NO, and CO, have potential roles in maintaining synaptic plasticity in the nervous system.

4. Role of Gasotransmitters in Neuropsychiatric Disease

4.1. MDD. MDD is a lifelong catastrophic mental disorder with high rates of morbidity and mortality [64]. The lifelong chronic–recurrent persistence of MDD is associated with very high economic and social burdens [65]. It is expected to be the second leading cause of disability worldwide by the World Health Organization (WHO) by 2020 [66]. The two gasotransmitters such as H_2S and NO are found to have some functions in MDD.

4.1.1. MDD and H_2S. H_2S is a toxic gas characterized by the smell of rotten eggs. Physiological concentrations of H_2S selectively increase NMDAR-induced responses as well as the advantageous induction of LTP [7]. One study demonstrated that H_2S can help maintain amygdala-dependent emotional memory by increasing the function of GluN2B-expressing NMDARs in the amygdala of rats [67]. Pathophysiological concentrations (200 pM) of sodium hydrogen sulfate (NaHS), an H_2S donor, stimulates seizure-like events in rats *in vivo* and *in vitro*, which may be due to increased neuronal excitation [68]. Previous studies indicated that H_2S might improve depressive and anxiety-related behaviors in nonstressed rats and mice, but the effects of H_2S on MDD animal models and the potential mechanism behind these effects are unknown [69]. To understand the actions and underlying mechanisms of H_2S related to depressive-like behavior, a recent study (intraperitoneally) injected the H_2S donor NaHS or administered inhaled H_2S in a chronic unpredictable mild stress (CUMS) model. The role of the mechanistic target of rapamycin (mTOR) signaling pathway and glutamate receptors (Figure 2) in the antidepressant effects of H_2S was evaluated [70]. The results indicated that a deficiency in endogenous H_2S in the hippocampus is responsible for the abnormal behaviors associated with CUMS, whereas enhancing hippocampal H_2S levels by the administration of NaHS or inhalation of H_2S could correct the depressive-like behaviors of rats within a few hours. This suggests that H_2S could function as a rapid-onset antidepressant. Additionally, H_2S could counteract the loss of

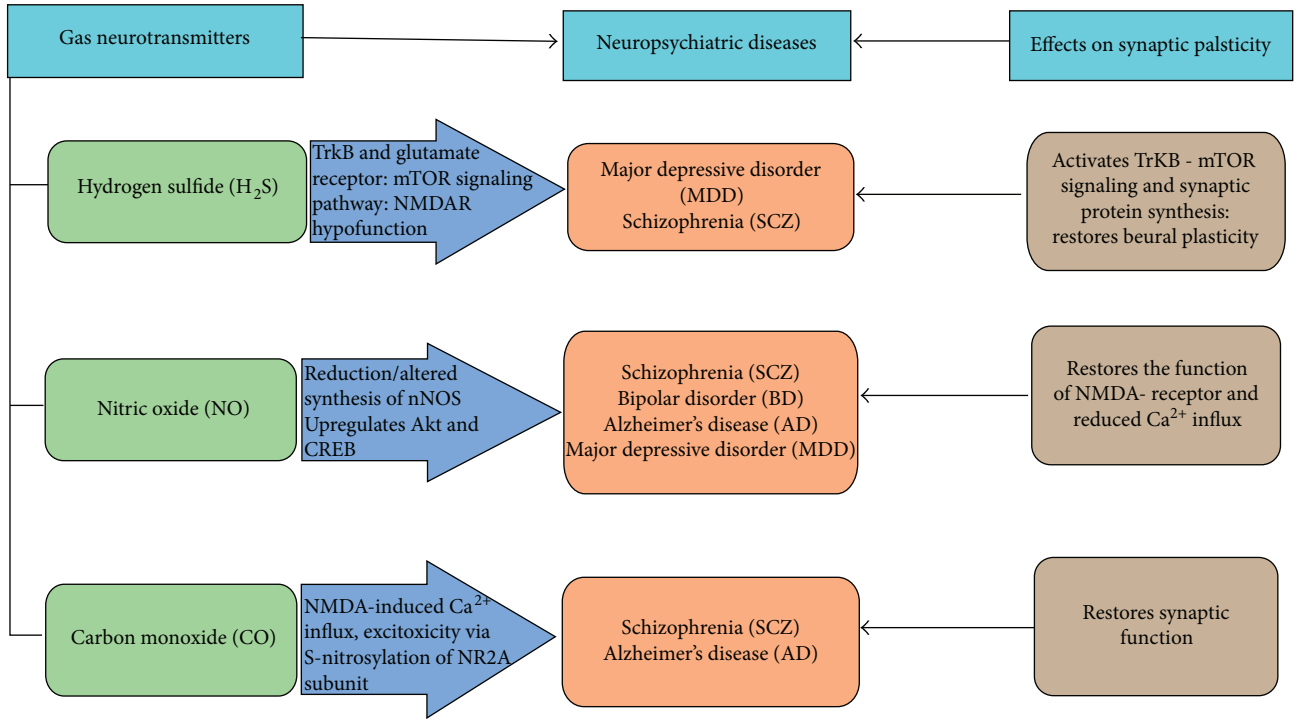


Figure 2: Role of gas neurotransmitters in neuropsychiatric diseases. The three gas neurotransmitters such as hydrogen sulfide (H_2S), nitric oxide (NO), and carbon dioxide (CO) have a role in neuropsychiatric conditions such as major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BD), and Alzheimer's disease (AD) to maintain proper synaptic plasticity as well as neural homeostasis. H_2S has a role in tropomyosin receptor kinase B (TrKB) and glutamate as well as mechanistic targets of rapamycin (mTOR) signaling pathways, and it activates the TrKB-mTOR signaling pathway as well as synaptic protein in MDD. NO has a role in the regulation of altered synthesis of nNOS as well as upregulates Akt and cyclic AMP (cAMP) response element binding (CREB) protein which restores function in *N*-methyl-D aspartate (NMDA) receptor and reduces Ca^{2+} influx in schizophrenia, MDD, and AD. CO has a role in NMDA-induced calcium ion (Ca^{2+}) influx or excitotoxicity via S-nitrosylation of antiglutamate receptor NMDAR2A (NR2A) subunit and restores synaptic function in AD and SCZ. However, these gas neurotransmitters work on various ways to maintain or restore synaptic plasticity in these neuropsychiatric diseases.

dendritic spines in the hippocampus that is associated with CUMS [70].

BDNF induces traditional antidepressant actions, and BDNF deletion in the hippocampus weakens antidepressant behavioral responses [71]. Some studies demonstrated that H_2S reversed the decrease in tropomyosin receptor kinase B (TrKB) receptors induced by CUMS, demonstrating the pivotal role of neurotrophic signaling in the antidepressant effects of H_2S. These findings are consistent with observations that H_2S exerted neuroprotective effects against formaldehyde-induced toxicity in PC12 cells via the BDNF–TrKB pathway [72]. This suggests that the synaptogenesis induced by glutamate receptor activation requires the release of BDNF to activate TrKB-mTOR signaling and synaptic protein synthesis (Figure 2). In another study, it was unclear whether the peripheral effects of H_2S played a role in the antidepressant responses; thus, additional studies are needed [70]. Nevertheless, this study also demonstrated that the acute application of H_2S, via either the H_2S donor NaHS or H_2S gas inhalation, induced robust antidepressant effects that were mediated by activation of the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway followed by the enhanced synthesis of synaptic proteins containing postsynaptic density protein 95 (PSD95) and synaptophysin. H_2S also increases the levels of TrKB receptors, which further increases the activity of the GluR1 and GluR2 subunits of AMPARs. An improved understanding of the roles of H_2S could provide insight into potential therapeutic interventions for depression [70].

Ketamine is a noncompetitive blocker of NMDAR that also stimulates the mTOR signaling pathway and subsequently increases the synthesis of the proteins involved in synapses to induce fast-acting antidepressant effects [73]. A study on ketamine-induced antidepressant effects provided an opportunity to explore the ability of new antidepressants with rapid-acting effects to provide sustained relief and fewer side effects. Various studies have demonstrated a link between H_2S and the mTOR signaling pathway. A recent study demonstrated that H_2S could decrease smoking-induced autophagic cell death by activating mTOR [74]. A novel H_2S-releasing molecule GYY4137 (water-soluble, slow-releasing H_2S donor) likely protected against high glucose-induced cytotoxicity by activating the mTOR signaling pathway in H9C2 (embryonic cardiomyocyte cell line) cells [75]. Additionally, H_2S ameliorated hepatic ischemia/reperfusion injury by stimulating phosphorylation of the pyruvate dehydrogenase kinase 1 (PDK-1)/Akt (protein kinase B)/mTOR/70 kDa ribosomal protein S6 kinase

(p70S6K) axis [76]. The effects of H_2S on mTOR activation are consistent with the mechanism of rapid-onset antidepressants [70].

H_2S is a gasotransmitter that activates the TrKB or mTOR signaling pathways to exert antidepressant effects that are indirectly associated with synaptic protein synthesis or restoration of synaptic plasticity in MDD.

4.1.2. MDD and NO. NO is a highly diffusible and reactive molecule that is synthesized and released with the help of NOSs during the conversion of arginine into citrulline, generating NO in the process [77]. NO mediates the effects of various neurotransmitters, such as norepinephrine, serotonin, glutamate, and dopamine, and thereby plays an essential role in the neurobiology of major depression. Modified NO levels in various brain regions, cerebrospinal fluid (CSF), blood, and exhaled gas have been reported in depression [78]. A meta-analysis revealed disorders in neurooxidative pathways in major depression [79]. Major depression is associated with nitrosative stress, as marked by elevated iNOS function and nitration, as well as by protein nitrosylation [80]. In depression, both neurooxidative and neuronitrative pathways may cause neuroprogression, such as the neuronal dysfunctions caused by oxidative pathways following enhanced neurotoxicity and cytotoxicity, disorders in synaptic plasticity, and reduced neuroprotection [81].

Postmortem studies of patients with MDD revealed reduced neuronal NO synthase levels in the locus coeruleus and a lower number of density of NO synthase-immunoreactive neurons in the hypothalamic nuclei of patients compared with healthy controls [82]. When peripheral NO levels were measured in MDD, some studies reported increased levels [83], whereas other studies found no change [84]. In medication-free depression, various studies found reduced NO levels [85]. In MDD, NO levels were reduced in drug-free patients experiencing depressive episodes in one study [85], but they were either increased or unchanged in another study [84]. Lu et al. demonstrated that NO levels were much higher in MDD patients but then decreased after antidepressant treatment. In the same study, the levels of amino acids, such as citrulline and arginine, were estimated as an index of NO synthesis [78]. In another study, elevated plasma NO levels were reported in male rat models of chronic and unpredictable stress as well as in first-episode MDD patients [86]. The plasma levels of NO metabolites, such as nitrite and nitrate, which reflect plasma NO levels, are also increased in depression [84]. One study described that elevated plasma NO levels in melancholic MDD patients are persistent [78]. This is consistent with previous reports, which also found increased NO plasma levels in MDD patients [87]. Additionally, the elevated NO plasma levels may be associated with suicide attempts in these patients. Modified glutamatergic and decreased GABAergic activity and NO neurotransmission were reported in various brain systems in depression, and this may have a critical effect on the neuronal functions associated with stress responses and mood maintenance [78].

NO is an essential gasotransmitter for neuronal homeostasis, and its upregulation is linked with MDD found in some studies above. Maintaining physiological concentrations of NO could be an effective therapeutic option in MDD.

4.2. SCZ. SCZ is a complex psychiatric illness caused by dysregulation of multiple brain neurotransmitter systems, such as those involving dopamine, glutamate, GABA, serotonin, and acetylcholine. Hence, modifications to these neurotransmitter systems [88] have led to hypotheses centering on the expression and functions of neurotransmitter receptors as critical elements of the pathophysiology of this condition; assimilation of signaling mediated by various neurotransmitter receptors is a pivotal step in achieving the functional interactions of receptor activation [89]. Subsequently, modifications of signal integration pathways may have a role to the pathophysiology of SCZ [88]. Gasotransmitters such as H_2S, NO, and CO have some roles in SCZ.

4.2.1. SCZ and NO. NO is associated with synaptic plasticity, neural plasticity, and cognition [90]. It bolsters the survival and differentiation of neurons as well as exhibits long-lasting events by maintaining transcription factors and altering gene expression. Lower concentrations of NO induce neuroprotective effects and support physiological signaling events, leading to neurotransmission and vasodilatation. In contrast, higher concentrations promote inflammatory effects and are neurotoxic [91]. It was hypothesized that NO could act as a retrograde messenger at synapses, transmitting signals from target neurons back to the synapses and maintaining synaptic plasticity. These same characteristics also allow NO to signal to any local compartment and to cells with defective synaptic activity and NOS expression [92]. Recent evidence revealed roles for NO and related molecules in the pathogenesis of SCZ. Changes in various effects of NO in CNS development may result in neurodevelopmental changes involved in SCZ [92]. NO is associated with many processes in the brain, such as the maintenance of synaptic plasticity, the release of mediators, and the development of nervous tissue [93].

Russian scientists Averbukh et al. (1966) and Bulba et al. (1968) first hypothesized that NO was involved in the onset of SCZ [94]. Studies reporting elevated levels of NO in the postmortem brain tissue [95] and plasma [96] of patients with SCZ also support a link between NOS activity and SCZ. The amount of nNOS differs in patients with SCZ and healthy controls [97]; yet, this issue is conflicted. The nNOS levels in the cortex of the cerebelli of patients with SCZ did not differ from the levels found in those of healthy controls in a study performed by Doyle and Slater in 1995 [98]. In another study, enhanced NO synthase activity was detected in Purkinje cells and the dentate nucleus of patients with SCZ but not with depression [99]. However, data regarding the presence of NOS in the neocortex are inconsistent [100]. Although the upregulated expression of nNOS was reported in the prefrontal cortex in SCZ [100], contrasting data have also been published. Striking data were carried out in the period of investigations of neurons of hypothalamus. The downregulation of nNOS-containing neurons was reported in the periventricular nucleus of patients with SCZ and affective disorders [101]. It was reported that NO in

the hypothalamus maintains the synthesis and release of the hormones that maintain the hypothalamic–pituitary–adrenal system (HPAS), including oxytocin, vasopressin, and corticoliberin. The altered production and release of these peptides leads to hyperactivation of HPAS in patients with SCZ [102].

NO levels have also been measured in biological fluids from SCZ patients. The level of NOS and its metabolites in the blood of patients with SCZ and depression has been assessed in many studies, and the results are conflicting [92]. A meta-analysis performed by Maia-de-Oliveira et al. found no significant difference in the NO levels of patients with SCZ and healthy controls. However, higher levels of NO were found in patients treated with antipsychotics, highlighting the influence of these drugs on the metabolism of NOS [103]. Therefore, the enhanced formation of NO does not seem to be caused by NMDARs. This suggests that AMPARs likely play an important role, especially as they are expressed at high levels in patients with SCZ [104]. The subsequent release of NO results in disturbed synaptogenesis and synaptic remodeling as well as in synaptic membrane modification [105].

Antipsychotics modify NO metabolism in the brain. For example, haloperidol suppresses nNOS activity [106]. Hence, the long-term administration of this drug results in nNOS hyperactivity in the striatum of rats [107]. The authors of this study demonstrated that late modification of nNOS activity in the neostriatum during antipsychotic treatment plays an important role in the pathogenesis of late dyskinesia. It is worth repeating that nNOS activity is higher in the plasma of patients with SCZ receiving antipsychotics compared with healthy controls [103]. These studies call into question the influence of nNOS activity in the brains of patients with SCZ [108]. The effects of antipsychotics on other NOS isoforms have also been studied. Clozapine can prevent iNOS activity and reduce microglial inflammation and NO levels in the brain [109]. The effects of antipsychotics on NO metabolism restore the normal function of NMDARs [92].

In summary, SCZ is a neuropsychiatric disorder in which normal synaptic plasticity is hampered. NO plays important roles in maintaining synaptic functions and synaptic plasticity in account of maintaining proper neuronal functioning.

4.2.2. SCZ, H_2S, and CO. CBS-derived H_2S is needed for amygdalar synaptic plasticity and fear conditioning in rats. In particular, inhibiting the function of amygdalar CBS prevented activity-stimulated H_2S production, blocked LTP initiation, and altered cued fear memory in rats [110]. Treatment with an H_2S donor corrected the LTP and memory impairments caused via CBS inhibition. This CBS inhibition was related to the maintenance of NMDAR function, as the NMDAR-supported synaptic response was lower when CBS was inhibited and the use of a H_2S donor increased the amplitude of the NMDAR EPSPs (5-enolpyruvylshikimate-3-phosphate) to a level comparable to those of the normal controls. This suggests that H_2S homeostasis in the brain is critical for the generation of synaptic plasticity and memory. S-Adenosylmethionine (SAM) stimulates CBS activity; it combines with the regulatory C-terminal domain of CBS to activate the generation of endogenous H_2S. Nevertheless, the mechanisms by which CBS inhibition alters amygdalar synaptic plasticity and memory require further investigation. Activation of NMDAR modulates synaptic plasticity, learning, and memory, and NMDAR hypofunction (Figure 2) was linked to cognitive deficits in aging as well as other psychiatric disorders, such as SCZ [110].

One study showed that prenatal exposure to CO leads to a variety of neurological effects. Lower concentrations of CO lead to a variety of neurobehavioral disorders in rat offspring. Prenatal CO exposure also hampers various neurotransmitters in the growing brains of male rats; low concentrations altered the mesolimbic dopaminergic function and sexual behavior [111]. Changes in cerebellar catecholamines linked these changes to deficits in motor test performance, learning, and memory, as determined by the reduced total GABA content in the cerebelli of 10-day-old rats exposed to CO prenatally. This suggests that GABAergic neurons may have a specific role in CO toxicity. Another study demonstrated that GABAergic neurons may be specifically vulnerable to CO toxicity. Therefore, GABA signaling is modified in neurological disorders, such as SCZ [111]. HO-1 expression in SCZ can be increased by oxidative and inflammatory stimuli [112]. The selective overexpression of HO-1 in the astrocytes of transgenic mice resulted in oxidative stress, lower neuronal reelin content, increased dopamine and serotonin concentrations in the basal ganglia, decreased D1 receptor binding in the nucleus acumens, and altered hippocampal cytoarchitectures. These pathological changes were related to enhanced co-motor activity and reduced proton pump inhibitors but did not affect anxiety or motor balance [113].

H_2S and CO have a potential role in neuronal homeostasis, and maintaining proper amounts of these gasotransmitters is a crucial factor in case of SCZ.

4.3. BD. BD is a severe neuropsychiatric condition that results in repeated episodes of mania, which are pathologically energized states characterized by poor judgment, euphoria, irritability, and in depressive episodes, which are characterized by dispiriting moods, decreased energy, volitional states, and decreased cognitive capacity [114]. The gasotransmitter NO is related to the BD which is briefly discussed below.

4.3.1. BD and NO. Modified NO signaling, which directly affects neurotransmitter release and synaptic plasticity cascades, has been demonstrated in BD. Lithium maintains NO levels in preclinical models. However, the effects of lithium ion NO levels have not been studied in humans [115]. Upregulated NO levels were reported during various mood states [116], particularly depressive episodes [117]. The NO pathway is particularly important in neuropsychiatric disorders. Altered NO levels affect neurotransmitter release [90] and synaptic plasticity [118]. High concentrations of NO have dose-dependent neurotoxic effects, whereas physiological concentrations play neuromodulatory and neuroprotective roles [91]. The neuroprotective effects of NO include reducing Ca^{2+} influx and subsequent cell death (Figure 2) [119]. Additionally, NO upregulates

the expression of the neuroprotective proteins Akt and CREB (Figure 2) [120] and the potent antioxidant bilirubin [121].

NO effects are persistent with neuroprotective as well as neurotrophic roles of lithium [122]. Lithium is the standard and first-line treatment option for BD [123]. Its mechanism of action is complex and involves multiple intracellular signaling pathways. Various animal studies have revealed that lithium maintains central and peripheral NO levels [124] and significantly increases NO levels in BD depression after 6 weeks of treatment. However, there was no marked difference in NO levels between unmedicated BD patients and matched healthy controls [122]. These experiments suggest that NO levels may be maintained by lithium in humans. Along these lines, an increasing body of preclinical evidence suggests that lithium can directly target NO signaling [124]. For example, lithium upregulates *NOS* messenger RNA (mRNA) expression in glial cultured cells [125], the hypothalamus [126], and the hippocampus [127] and also increases cortical NO metabolites in rodents. Other preclinical studies showed that lithium reduces NO metabolites [128] in rat neural tissues [129]. The upregulated NO levels were not associated with clinical improvement, increasing the possibility that the effects of lithium ion NO may be an epiphenomenon or an intermediate pathway for the antidepressant effect [115].

In a recent study, the plasma NO levels in BD patients did not differ from those of healthy controls [115]. In terms of mood disorders, studies on NO have yielded mixed results. At the same time, several studies reported enhanced NO levels in BD [116], and another study that analyzed NO levels during a depressive episode in BD [117] showed elevated NO metabolite levels in subjects with BD receiving multiple medications that can influence NO [103]. The fact that the sample contained drug-free patients with a short duration of illness means that it is possible that NO plays a more important role in BD late in the course of the illness, after patients have been exposed to chronic insults such as repetitive episodes, medications, and comorbidities. Additionally, the number of previous mood episodes was positively correlated with NO levels in BD [130]. These studies may support a crucial role for NO signaling in the trophic and neuroprotective effects of lithium in BD and other neuropsychiatric disorders [115].

In conclusion, the gasotransmitter NO plays a pivotal role in maintaining neural plasticity and proper neuronal functioning in the service of preserving the activity of the CNS in BD.

4.4. AD. AD is characterized by the loss of neurons and synapses in the hippocampus, cerebral cortex, and subcortical regions, as well as the formation of amyloid beta (Aβ) plaques and neurofibrillary lesions. The main protein component of plaques is amyloid-β, which is derived from the proteolytic cleavage of amyloid precursor protein (APP). Mutations associated with early-onset of familial AD increase Aβ production. Aβ isolated directly from human AD brains caused impaired synaptic plasticity and memory in rodents [131]. Synaptic activity and chronic sleep restriction increase the amount of Aβ in brain and intestinal fluid, as well as plaque formation in APP transgenic mice [132]. AD is related with some gasotransmitters such as CO and NO, which is discussed briefly in the following subsections.

4.4.1. AD and CO. As discussed above, mammalian tissues express two isoforms of heme oxygenase: HO-1 and HO-2. The third isoform, HO-3, is a retrotransposition of the *HO-2* gene and is only found in rats [133]. The basal expression of HO-1 in the normal brain is restricted to small groups of scattered neurons and neuroglia [134], whereas HO-2 is more broadly expressed across the neuraxis [60]. HO-1 is a 32 kDa protein that catalyzes the breakdown of heme to free iron, CO, and biliverdin. In "stressed" astroglia, HO-1 hyperactivity stimulates mitochondrial iron sequestration and macroautophagy, which may be responsible for the pathological iron accumulation and bioenergetic failure observed in AD as well as in other neurodevelopmental conditions. The expression of glial HO-1 may also affect neuroplasticity and cell survival by modulating the brain sterol metabolism and the proteasomal deterioration of neurotoxic proteins [135].

HO-1 immunoreactivity in glia increases progressively as aging progresses in the normal human brain [136]. HO-1 deteriorates as neural tissue senesces, which may be responsible for the biogenesis of the corpora amylacea and glycoprotein-rich inclusions generally encountered in aging mammalian cells [137]. The number of glial fibrillary acid protein- (GFAP-) positive astrocytes that express HO-1 is increased significantly in the hippocampus and cerebral cortex of patients with AD compared with age-matched, nondemented controls. An excessive increase in glial HO-1 levels is already apparent in the brains of subjects with mild cognitive impairment (MCI), which is a common precursor or indication of incipient AD [138]. In the temporal cortex of patients with MCI, the number of astrocytes with immunoreactivity for HO-1 is related to the degree of neurofibrillary pathology and also the reductions in scores on tests of global cognition, episodic memory, semantic memory, and working memory. Similarly, HO-1 expression in astroglia is associated with lower scores for global cognition, perceptual speed, and semantic memory.

Elevated CO is found in the above studies in AD, and regulating physiological levels of CO could be a therapeutic option in case of AD.

4.4.2. AD and NO. Deficits in synaptic plasticity are increasingly recognized as causes of memory loss in AD [139]. However, the early mechanisms driving synaptic pathophysiology are poorly understood. Short-term plasticity and long-term plasticity are calcium-dependent processes that can be altered by second messengers, such as NO. NO is produced by NOS via NMDAR-mediated calcium entry [140]. NO signaling is involved in neurodegenerative diseases via the formation of reactive nitrogen species and cGMP signaling cascades [141]. NO also has neuroprotective effects, as shown in AD mouse models in which it reduces cell loss and tau pathology [142]. In AD models, NO can be altered via various mechanisms. For example, the NMDAR-mediated calcium entry that activates NOS is augmented by abnormal ryanodine receptor- (RyR-) mediated calcium-induced calcium release [143]. NOS protein levels and RyR levels are also

increased in both AD mouse models and human AD brains [144]. In presynaptic AD mice, these conditions that amplify NO levels occur alongside exaggerated hippocampal synaptic depression. These deficits occur when homeostasis is challenged, such as in the presence of reduced RyR-calcium release. Although the hippocampal network and cognitive performance appear normal, they clearly are not [145].

In one study, the primary site of NO regulation in 3×-Tg-AD mice was the presynaptic terminals, where it increased evoked and spontaneous vesicle release, as determined by PPF assays and spontaneous vesicle-release properties [146]. In this study, NO could increase transmitter release via cGMP signaling as well as the S-nitrosylation of synaptic proteins, which increases the presynaptic binding of syntaxin to VAMP and SNAPZS [147]. NO also alters the magnitude of vesicular release by converting reserve pool vesicles into easily releasable vesicles [148]. NO can also increase RyR channel opening, possibly via S-nitrosylation. The opposing interactions between enhanced RyR-calcium signaling and increased nNOS expression in AD neurons can sustain enhanced NO production or synthesis and also increase presynaptic gain. Postsynaptically, the neuroprotective characteristics of NO curb the excessive NMDAR-induced calcium influx and excitotoxicity by causing S-nitrosylation of the antiglutamate receptor NMDAR2A (NR2A) subunit (Figure 2). At the same time, the S-nitrosylation of caspase-3, -8, and -9 decreases apoptosis. The enhanced nNOS levels and NO activity in AD brains may have a neuroprotective role, as demonstrated by the selectively spared NOS-positive neurons in AD. Hence, constant increases in NO have harmful effects, such as oxidative stress, the fragmentation loss of synaptic functioning, and apoptosis [141].

In summary, AD is a major neuropsychiatric disorder, and the regulation of NO is essential for maintaining proper neuronal functioning and synaptic plasticity in the CNS during AD.

5. Future Directions

Gasotransmitters are the essential molecules that help regulate synaptic and neuroplasticity in the CNS. Three gas neurotransmitters, H_2S, NO, and CO, were discussed briefly. These gasotransmitters are related to neuropsychiatric conditions. For example, H_2S downregulation was involved with the progression of MDD in one study, but the molecular mechanisms by which reduced H_2S levels lead to MDD need to be studied further [69, 70]. In terms of other gasotransmitters, higher NO levels were reported in the postmortem brains of SCZ patients [103]; thus, downregulation or modified regulation could be a therapeutic option for treating SCZ. NO levels are also altered in BD patients, and this could facilitate the identification of therapies to treat these neuropsychiatric conditions. Additionally, increased levels of HO-1 or CO were observed in AD patients, which highlights how gasotransmitters may be involved with neuropsychiatric conditions and how regulating these gasotransmitters could help treat these disorders.

6. Conclusion

Maintaining synaptic plasticity is crucial for regulating neuronal health and homeostasis. Neuronal functioning declines over time or under stressful conditions whereas many reactive species can lead to different neuropsychiatric conditions, such as SCZ, MDD, BD, and AD. Several gasotransmitters, such as H_2S, NO, and CO, balance synaptic plasticity when the normal condition is altered directly or indirectly. However, as the mechanisms or pathways through which they act are poorly understood, further studies are needed. Because the up- or downregulation of these gasotransmitters is responsible for causing the pathological conditions that lead to neuropsychiatric diseases, the normalization of their levels could exert protective effects. Hence, ensuring that the levels of these gasotransmitters are appropriate could help in the treatment of neuropsychiatric conditions. Moreover, improvements in our understanding of these pathways may lead to the identification of new therapeutic options for these neuropsychiatric conditions.

Abbreviations

AD: Alzheimer's disease
AMPA: α-Amino-3-hydroxy-5-methyl-isoxazole-4-propanoic acid
AMPARs: α-Amino-3-hydroxy-5-methyl-isoxazole-4-propanoic acid receptors
Aβ: Amyloid beta
APP: Amyloid precursor protein
BD: Bipolar disorder
BDNF: Brain derivative neurotrophic factor
CA3: Cornu Ammonis 3
CaMKII: Calcium/calmodulin-dependent kinase II
CREB: Cyclic AMP response element binding protein
CO: Carbon monoxide
Ca^{2+}: Calcium ion
CBS: Cystathionine β-synthase
CSE: Cystathionine γ-lyase
CAT: Cysteine aminotransferase
cGMP: Cyclic guanosine monophosphate
cAMP: Cyclic adenosine monophosphate
CUMS: Chronic unpredictable mild stress
DAAO: D-Amino acid oxidase
DRG: Dorsal root ganglion
ERK: Extracellular signal-regulated kinase
EPAC: Exchange protein stimulated by cAMP
GABA: Gamma amino butyric acid
GFAP: Glial fibrillary acid protein
GSH: Glutathione
GSSH: Glutathione persulfide
H_2S_n: Polysulfide
H_2S: Hydrogen sulfide
HO-1: Hemeoxygenase-1
HO-2: Hemeoxygenase-2
HO-3: Hemeoxygenase-3
HPAS: Hypothalamic–pituitary–adrenal system
JNK: C-Jun *N*-terminal kinase
LTP: Long-term potentiation

LTD: Long-term depression
MDD: Major depressive disorder
MAPK: Mitogen-activated protein kinases
3-MST: 3-Mercaptopyruvate sulfurtransferase
mTOR: Mechanistic target of rapamycin
mRNA: Messenger ribonucleic acid
MCI: Mild cognitive impairment
NMDA: *N*-Methyl-D-aspartate
NMDARs: *N*-Methyl-D-aspartate receptors
NO: Nitric oxide
NOS: Nitric oxide synthase
NaHS: Sodium hydrogen sulfate
NSCs: Neural stem cells
Nrf2: Nuclear factor erythroid 2-related factor 2
PKA: Protein kinase A
RyR: Ryanodine receptor
SCZ: Schizophrenia
SSRIs: Serotonin reuptake inhibitors
SAM: S-Adenosylmethionine
siRNA: Small interfering RNA
TrkB: Tropomyosin receptor kinase B
TRPA1: Transient receptor potential ankyrin 1
VGCC: Voltage-gated calcium channels
VEGF: Vascular endothelial growth factor
WHO: World Health Organization.

Conflicts of Interest

The authors reported no potential conflict of interests.

Acknowledgments

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (2018R1A2B6001123).

References

[1] A. Kumar, "Long-term potentiation at CA3–CA1 hippocampal synapses with special emphasis on aging, disease, and stress," *Frontiers in Aging Neuroscience*, vol. 3, pp. 1–20, 2011.

[2] T. V. P. Bliss and G. L. Collingridge, "A synaptic model of memory: long-term potentiation in the hippocampus," *Nature*, vol. 361, no. 6407, pp. 31–39, 1993.

[3] C. R. Bramham and E. Messaoudi, "BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis," *Progress in Neurobiology*, vol. 76, no. 2, pp. 99–125, 2005.

[4] R. C. Malenka and M. F. Bear, "LTP and LTD: an embarrassment of riches," *Neuron*, vol. 44, no. 1, pp. 5–21, 2004.

[5] E. P. Rico, D. B. Rosemberg, K. J. Seibt, K. M. Capiotti, R. S. Da Silva, and C. D. Bonan, "Zebrafish neurotransmitter systems as potential pharmacological and toxicological targets," *Neurotoxicology and Teratology*, vol. 33, no. 6, pp. 608–617, 2011.

[6] A. V. Yakovlev, E. D. Kurmasheva, R. Giniatullin, I. Khalilov, and G. F. Sitdikova, "Hydrogen sulfide inhibits giant depolarizing potentials and abolishes epileptiform activity of neonatal rat hippocampal slices," *Neuroscience*, vol. 340, pp. 153–165, 2017.

[7] K. Abe and H. Kimura, "The possible role of hydrogen sulfide as an endogenous neuromodulator," *Journal of Neuroscience*, vol. 16, no. 3, pp. 1066–1071, 1996.

[8] N. Hardingham, J. Dachtler, and K. Fox, "The role of nitric oxide in pre-synaptic plasticity and homeostasis," *Frontiers in Cellular Neuroscience*, vol. 7, pp. 1–19, 2013.

[9] C. Hölscher, "Nitric oxide, the enigmatic neuronal messenger: its role in synaptic plasticity," *Trends in Neurosciences*, vol. 20, no. 7, pp. 298–303, 1997.

[10] J. R. Steinert, T. Chernova, and I. D. Forsythe, "Nitric oxide signaling in brain function, dysfunction, and dementia," *The Neuroscientist*, vol. 16, no. 4, pp. 435–452, 2010.

[11] J. Jung, C. Na, and Y. Huh, "Alterations in nitric oxide synthase in the aged CNS," *Oxidative Medicine and Cellular Longevity*, vol. 2012, Article ID 718976, 7 pages, 2012.

[12] K. D. Poss and S. Tonegawa, "Reduced stress defense in heme oxygenase 1-deficient cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 20, pp. 10925–10930, 1997.

[13] C. F. Stevens and Y. Wang, "Reversal of long-term potentiation by inhibitors of haem oxygenase," *Nature*, vol. 364, no. 6433, pp. 147–149, 1993.

[14] M. P. Mattson, "Mitochondrial regulation of neuronal plasticity," *Neurochemical Research*, vol. 32, no. 4-5, pp. 707–715, 2007.

[15] H. J. Carlisle and M. B. Kennedy, "Spine architecture and synaptic plasticity," *Trends in Neurosciences*, vol. 28, no. 4, pp. 182–187, 2005.

[16] V. Todorova and A. Blokland, "Mitochondria and synaptic plasticity in the mature and aging nervous system," *Current Neuropharmacology*, vol. 15, no. 1, pp. 166–173, 2017.

[17] D. Mauceri, F. Gardoni, E. Marcello, and M. Di Luca, "Dual role of CaMKII-dependent SAP97 phosphorylation in mediating trafficking and insertion of NMDA receptor subunit NR2A," *Journal of Neurochemistry*, vol. 100, no. 4, pp. 1032–1046, 2007.

[18] X. Cheng, Z. Ji, T. Tsalkova, and F. Mei, "Epac and PKA: a tale of two intracellular cAMP receptors," *Acta Biochimica et Biophysica Sinica*, vol. 40, no. 7, pp. 651–662, 2008.

[19] A. A. Reichenberg, "The assessment of neuropsychological functioning in schizophrenia," *Dialogues in Clinical Neuroscience*, vol. 12, no. 3, pp. 383–392, 2010.

[20] V. M. Ho, J.-A. Lee, and K. C. Martin, "The cell biology of synaptic plasticity," *Science*, vol. 334, no. 6056, pp. 623–628, 2011.

[21] H. Park and M. Poo, "Neurotrophin regulation of neural circuit development and function," *Nature Reviews Neuroscience*, vol. 14, no. 1, pp. 7–23, 2013.

[22] M. Sasi, B. Vignoli, M. Canossa, and R. Blum, "Neurobiology of local and intercellular BDNF signaling," *Pflügers Archiv - European Journal of Physiology*, vol. 469, no. 5-6, pp. 593–610, 2017.

[23] B. Lu, G. Nagappan, X. Guan, P. J. Nathan, and P. Wren, "BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases," *Nature Reviews Neuroscience*, vol. 14, no. 6, pp. 401–416, 2013.

[24] N. W. Daw, P. S. G. Stein, and K. Fox, "The role of NMDA receptors in information processing," *Annual Review of Neuroscience*, vol. 16, no. 1, pp. 207–222, 1993.

[25] G. Voglis and N. Tavernarakis, "The role of synaptic ion channels in synaptic plasticity," *EMBO Reports*, vol. 7, no. 11, pp. 1104–1110, 2006.

[26] Y. Humeau, H. Shaban, S. Bissière, and A. Lüthi, "Presynaptic induction of heterosynaptic associative plasticity in the mammalian brain," *Nature*, vol. 426, no. 6968, pp. 841–845, 2003.

[27] A. L. Coon, D. R. Wallace, C. F. Mactutus, and R. M. Booze, "L-type calcium channels in the hippocampus and cerebellum of Alzheimer's disease brain tissue," *Neurobiology of Aging*, vol. 20, no. 6, pp. 597–603, 1999.

[28] T. Novkovic, T. Mittmann, and D. Manahan-Vaughan, "BDNF contributes to the facilitation of hippocampal synaptic plasticity and learning enabled by environmental enrichment," *Hippocampus*, vol. 25, no. 1, pp. 1–15, 2015.

[29] U. Shefa, S. G. Yeo, M. S. Kim et al., "Role of gasotransmitters in oxidative stresses, neuroinflammation, and neuronal repair," *BioMed Research International*, vol. 2017, Article ID 1689341, 15 pages, 2017.

[30] N. Shibuya, S. Koike, M. Tanaka et al., "A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells," *Nature Communications*, vol. 4, p. 1366, 2013.

[31] M. Lee, C. Schwab, S. Yu, E. McGeer, and P. L. McGeer, "Astrocytes produce the antiinflammatory and neuroprotective agent hydrogen sulfide," *Neurobiology of Aging*, vol. 30, no. 10, pp. 1523–1534, 2009.

[32] M. S. Vandiver, B. D. Paul, R. Xu et al., "Sulfhydration mediates neuroprotective actions of parkin," *Nature Communications*, vol. 4, p. 1626, 2013.

[33] Y. Kimura, Y. Mikami, K. Osumi, M. Tsugane, J. Oka, and H. Kimura, "Polysulfides are possible H_2S-derived signaling molecules in rat brain," *The FASEB Journal*, vol. 27, no. 6, pp. 2451–2457, 2013.

[34] S. Koike, K. Kawamura, Y. Kimura, N. Shibuya, H. Kimura, and Y. Ogasawara, "Analysis of endogenous H_2S and H_2S_n in mouse brain by high-performance liquid chromatography with fluorescence and tandem mass spectrometric detection," *Free Radical Biology & Medicine*, vol. 113, pp. 355–362, 2017.

[35] Y. Hatakeyama, K. Takahashi, M. Tominaga, H. Kimura, and T. Ohta, "Polysulfide evokes acute pain through the activation of nociceptive TRPA1 in mouse sensory neurons," *Molecular Pain*, vol. 11, no. 1, p. 24, 2015.

[36] Y. Kimura, Y. Toyofuku, S. Koike et al., "Identification of H_2S_3 and H_2S produced by 3-mercaptopyruvate sulfurtransferase in the brain," *Scientific Reports*, vol. 5, no. 1, article 14774, 2015.

[37] J. W. Hylin and J. L. Wood, "Enzymatic formation of polysulfides from mercaptopyruvate," *The Journal of Biological Chemistry*, vol. 234, no. 8, pp. 2141–2144, 1959.

[38] Y. Kimura, S. Koike, N. Shibuya, D. Lefer, Y. Ogasawara, and H. Kimura, "3-Mercaptopyruvate sulfurtransferase produces potential redox regulators cysteine- and glutathione-persulfide (Cys-SSH and GSSH) together with signaling molecules H_2S_2, H_2S_3 and H_2S," *Scientific Reports*, vol. 7, no. 1, article 10459, 2017.

[39] Y. Nagai, M. Tsugane, J.-I. Oka, and H. Kimura, "Hydrogen sulfide induces calcium waves in astrocytes," *The FASEB Journal*, vol. 18, no. 3, pp. 557–559, 2004.

[40] H. Kimura, "Hydrogen sulfide induces cyclic AMP and modulates the NMDA receptor," *Biochemical and Biophysical Research Communications*, vol. 267, no. 1, pp. 129–133, 2000.

[41] Y.-L. Li, P.-F. Wu, J.-G. Chen et al., "Activity-dependent sulfhydration signal controls N-methyl-D-aspartate subtype glutamate receptor-dependent synaptic plasticity *via* increasing d-serine availability," *Antioxidants & Redox Signaling*, vol. 27, no. 7, pp. 398–414, 2017.

[42] J. Garthwaite, "From synaptically localized to volume transmission by nitric oxide," *The Journal of Physiology*, vol. 594, no. 1, pp. 9–18, 2016.

[43] J. Prickaerts, N. P. Van Goethem, W. Gulisano, E. K. Argyrousi, A. Palmeri, and D. Puzzo, "Physiological and pathological processes of synaptic plasticity and memory in drug discovery: do not forget the dose-response curve," *European Journal of Pharmacology*, vol. 817, pp. 59–70, 2017.

[44] K. E. Hoque, R. P. Indorkar, S. Sammut, and A. R. West, "Impact of dopamine–glutamate interactions on striatal neuronal nitric oxide synthase activity," *Psychopharmacology*, vol. 207, no. 4, pp. 571–581, 2010.

[45] J. Garthwaite, S. L. Charles, and R. Chess-Williams, "Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain," *Nature*, vol. 336, no. 6197, pp. 385–388, 1988.

[46] D. S. Bredt and S. H. Snyder, "Nitric oxide, a novel neuronal messenger," *Neuron*, vol. 8, no. 1, pp. 3–11, 1992.

[47] E. Szabadits, C. Cserép, A. Szőnyi et al., "NMDA receptors in hippocampal GABAergic synapses and their role in nitric oxide signaling," *Journal of Neuroscience*, vol. 31, no. 16, pp. 5893–5904, 2011.

[48] G. K. Kolluru, X. Shen, S. C. Bir, and C. G. Kevil, "Hydrogen sulfide chemical biology: pathophysiological roles and detection," *Nitric Oxide*, vol. 35, pp. 5–20, 2013.

[49] R. Dingledine, K. Borges, D. Bowie, and S. F. Traynelis, "The glutamate receptor ion channels," *Pharmacological Reviews*, vol. 51, no. 1, pp. 7–61, 1999.

[50] J. Q. Wang, X.-P. Chu, M.-L. Guo et al., "Modulation of ionotropic glutamate receptors and acid-sensing ion channels by nitric oxide," *Frontiers in Physiology*, vol. 3, pp. 1–6, 2012.

[51] B. H. Tan, P. T. H. Wong, and J. S. Bian, "Hydrogen sulfide: a novel signaling molecule in the central nervous system," *Neurochemistry International*, vol. 56, no. 1, pp. 3–10, 2010.

[52] J. Blasko, K. Fabianova, M. Martoncikova, D. Sopkova, and E. Racekova, "Immunohistochemical evidence for the presence of synaptic connections of nitrergic neurons in the rat rostral migratory stream," *Cellular and Molecular Neurobiology*, vol. 33, no. 6, pp. 753–757, 2013.

[53] R. M. Cooke, R. Mistry, R. A. J. Challiss, and V. A. Straub, "Nitric oxide synthesis and cGMP production is important for neurite growth and synapse remodeling after axotomy," *Journal of Neuroscience*, vol. 33, no. 13, pp. 5626–5637, 2013.

[54] A. A. Steiner, E. Colombari, and L. G. S. Branco, "Carbon monoxide as a novel mediator of the febrile response in the central nervous system," *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 277, no. 2, pp. R499–R507, 1999.

[55] M. D. Maines, "Carbon monoxide: an emerging regulator of cGMP in the brain," *Molecular and Cellular Neuroscience*, vol. 4, no. 5, pp. 389–397, 1993.

[56] J. F. Ewing and M. D. Maines, "In situ hybridization and immunohistochemical localization of heme oxygenase-2 mRNA and protein in normal rat brain: differential distribution of isozyme 1 and 2," *Molecular and Cellular Neuroscience*, vol. 3, no. 6, pp. 559–570, 1992.

[57] G. S. Marks, J. F. Brien, K. Nakatsu, and B. E. McLaughlin, "Does carbon monoxide have a physiological function?," *Trends in Pharmacological Sciences*, vol. 12, no. 5, pp. 185–188, 1991.

[58] T. Morita, M. A. Perrella, M.-E. Lee, and S. Kourembanas, "Smooth muscle cell-derived carbon monoxide is a regulator of vascular cGMP," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, no. 5, pp. 1475–1479, 1995.

[59] C. S. F. Queiroga, A. Vercelli, and H. L. A. Vieira, "Carbon monoxide and the CNS: challenges and achievements," *British Journal of Pharmacology*, vol. 172, no. 6, pp. 1533–1545, 2015.

[60] A. Verma, D. J. Hirsch, C. E. Glatt, G. V. Ronnett, and S. H. Snyder, "Carbon monoxide: a putative neural messenger," *Science*, vol. 259, no. 5093, pp. 381–384, 1993.

[61] S.-Y. Hung, H.-C. Liou, K.-H. Kang, R.-M. Wu, C.-C. Wen, and W.-M. Fu, "Overexpression of heme oxygenase-1 protects dopaminergic neurons against 1-methyl-4-phenylpyridinium-induced neurotoxicity," *Molecular Pharmacology*, vol. 74, no. 6, pp. 1564–1575, 2008.

[62] N. Dreyer-Andersen, A. S. Almeida, P. Jensen et al., "Intermittent, low dose carbon monoxide exposure enhances survival and dopaminergic differentiation of human neural stem cells," *PLoS One*, vol. 13, no. 1, article e0191207, 2018.

[63] Y. K. Choi, C.-K. Kim, H. Lee et al., "Carbon monoxide promotes VEGF expression by increasing HIF-1α protein level via two distinct mechanisms, translational activation and stabilization of HIF-1α protein," *Journal of Biological Chemistry*, vol. 285, no. 42, pp. 32116–32125, 2010.

[64] R. C. Kessler, P. Berglund, O. Demler et al., "The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R)," *JAMA*, vol. 289, no. 23, pp. 3095–3105, 2003.

[65] M. Miret, J. L. Ayuso-Mateos, J. Sanchez-Moreno, and E. Vieta, "Depressive disorders and suicide: epidemiology, risk factors, and burden," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 10, pp. 2372–2374, 2013.

[66] C. J. L. Murray and A. D. Lopez, "Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study," *The Lancet*, vol. 349, no. 9064, pp. 1498–1504, 1997.

[67] C.-M. Wang, Y.-J. Yang, J.-T. Zhang et al., "Regulation of emotional memory by hydrogen sulfide: role of GluN2B-containing NMDA receptor in the amygdala," *Journal of Neurochemistry*, vol. 132, no. 1, pp. 124–134, 2015.

[68] Y. Luo, P. F. Wu, J. Zhou et al., "Aggravation of seizure-like events by hydrogen sulfide: involvement of multiple targets that control neuronal excitability," *CNS Neuroscience & Therapeutics*, vol. 20, no. 5, pp. 411–419, 2014.

[69] W.-L. Chen, B. Xie, C. Zhang et al., "Antidepressant-like and anxiolytic-like effects of hydrogen sulfide in behavioral models of depression and anxiety," *Behavioural Pharmacology*, vol. 24, no. 7, pp. 590–597, 2013.

[70] X.-Y. Hou, Z.-L. Hu, D.-Z. Zhang et al., "Rapid antidepressant effect of hydrogen sulfide: evidence for activation of mTORC1-TrkB-AMPA receptor pathways," *Antioxidants & Redox Signaling*, vol. 27, no. 8, pp. 472–488, 2017.

[71] L. M. Monteggia, M. Barrot, C. M. Powell et al., "Essential role of brain-derived neurotrophic factor in adult hippocampal function," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 29, pp. 10827–10832, 2004.

[72] J.-M. Jiang, C.-F. Zhou, S.-L. Gao et al., "BDNF-TrkB pathway mediates neuroprotection of hydrogen sulfide against formaldehyde-induced toxicity to PC12 cells," *PLoS One*, vol. 10, no. 3, article e0119478, 2015.

[73] N. Li, B. Lee, R.-J. Liu et al., "mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists," *Science*, vol. 329, no. 5994, pp. 959–964, 2010.

[74] X. Zhou, G. An, and J. Chen, "Hydrogen sulfide improves left ventricular function in smoking rats via regulation of apoptosis and autophagy," *Apoptosis*, vol. 19, no. 6, pp. 998–1005, 2014.

[75] W. Wei, X. Hu, X. Zhuang, L. Liao, and W. Li, "GYY4137, a novel hydrogen sulfide-releasing molecule, likely protects against high glucose-induced cytotoxicity by activation of the AMPK/mTOR signal pathway in H9c2 cells," *Molecular and Cellular Biochemistry*, vol. 389, no. 1-2, pp. 249–256, 2014.

[76] S. Shimada, M. Fukai, K. Wakayama et al., "Hydrogen sulfide augments survival signals in warm ischemia and reperfusion of the mouse liver," *Surgery Today*, vol. 45, no. 7, pp. 892–903, 2015.

[77] O. W. Griffith and D. J. Stuehr, "Nitric oxide synthases: properties and catalytic mechanism," *Annual Review of Physiology*, vol. 57, no. 1, pp. 707–734, 1995.

[78] Y.-R. Lu, Y. Zhang, Y.-B. Rao et al., "The changes in and relationship between plasma nitric oxide and corticotropin-releasing hormone in patients with major depressive disorder," *Clinical and Experimental Pharmacology and Physiology*, vol. 45, no. 1, pp. 10–15, 2018.

[79] T. Liu, S. Zhong, X. Liao et al., "A meta-analysis of oxidative stress markers in depression," *PLoS One*, vol. 10, no. 10, article e0138904, 2015.

[80] P. Gałecki, E. Gałecka, M. Maes et al., "The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder," *Journal of Affective Disorders*, vol. 138, no. 3, pp. 360–366, 2012.

[81] B. Kanchanatawan, S. Tangwongchai, A. Sughondhabhirom et al., "Add-on treatment with curcumin has antidepressive effects in Thai patients with major depression: results of a randomized double-blind placebo-controlled study," *Neurotoxicity Research*, vol. 33, no. 3, pp. 621–633, 2018.

[82] H. G. Bernstein, A. Heinemann, D. Krell et al., "Hypothalamic nitric oxide synthase in affective disorder: focus on the suprachiasmatic nucleus," *Cellular and Molecular Biology*, vol. 51, no. 3, pp. 279–284, 2005.

[83] E. Suzuki, G. Yagi, T. Nakaki, S. Kanba, and M. Asai, "Elevated plasma nitrate levels in depressive states," *Journal of Affective Disorders*, vol. 63, no. 1–3, pp. 221–224, 2001.

[84] Y.-K. Kim, J.-W. Paik, S.-W. Lee, D. Yoon, C. Han, and B.-H. Lee, "Increased plasma nitric oxide level associated with suicide attempt in depressive patients," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 30, no. 6, pp. 1091–1096, 2006.

[85] R. G. García, J. G. Zarruk, C. Barrera et al., "Plasma nitrate levels and flow-mediated vasodilation in untreated major depression," *Psychosomatic Medicine*, vol. 73, no. 4, pp. 344–349, 2011.

[86] Y.-R. Lu, X. Y. Fu, L. G. Shi et al., "Decreased plasma neuroactive amino acids and increased nitric oxide levels in

melancholic major depressive disorder," *BMC Psychiatry*, vol. 14, no. 1, p. 123, 2014.

[87] S.-F. Gao, Y.-R. Lu, L.-G. Shi et al., "Nitric oxide synthase and nitric oxide alterations in chronically stressed rats: a model for nitric oxide in major depressive disorder," *Psychoneuroendocrinology*, vol. 47, pp. 136–140, 2014.

[88] A. J. Funk, R. E. McCullumsmith, V. Haroutunian, and J. H. Meador-Woodruff, "Abnormal activity of the MAPK- and cAMP-associated signaling pathways in frontal cortical areas in postmortem brain in schizophrenia," *Neuropsychopharmacology*, vol. 37, no. 4, pp. 896–905, 2012.

[89] D. W. Volk, S. M. Eggan, and D. A. Lewis, "Alterations in metabotropic glutamate receptor 1α and regulator of G protein signaling 4 in the prefrontal cortex in schizophrenia," *American Journal of Psychiatry*, vol. 167, no. 12, pp. 1489–1498, 2010.

[90] H. Prast and A. Philippu, "Nitric oxide as modulator of neuronal function," *Progress in Neurobiology*, vol. 64, no. 1, pp. 51–68, 2001.

[91] V. Calabrese, C. Mancuso, M. Calvani, E. Rizzarelli, D. A. Butterfield, and A. M. Giuffrida Stella, "Nitric oxide in the central nervous system: neuroprotection versus neurotoxicity," *Nature Reviews Neuroscience*, vol. 8, no. 10, pp. 766–775, 2007.

[92] R. F. Nasyrova, D. V. Ivashchenko, M. V. Ivanov, and N. G. Neznanov, "Role of nitric oxide and related molecules in schizophrenia pathogenesis: biochemical, genetic and clinical aspects," *Frontiers in Physiology*, vol. 6, pp. 1–16, 2015.

[93] S. M. Gibbs, "Regulation of neuronal proliferation and differentiation by nitric oxide," *Molecular Neurobiology*, vol. 27, no. 2, pp. 107–120, 2003.

[94] M. L. Averbukh, A. F. Kas'ko, E. S. Nikolenko, and I. I. Rybas, "On the diagnostic significance of Black's reaction in psychiatric patients," *Laboratornoe Delo*, vol. 5, pp. 289–291, 1965.

[95] J. K. Yao, S. Leonard, and R. D. Reddy, "Increased nitric oxide radicals in postmortem brain from patients with schizophrenia," *Schizophrenia Bulletin*, vol. 30, no. 4, pp. 923–934, 2004.

[96] M. Zhang, Z. Zhao, L. He, and C. Wan, "A meta-analysis of oxidative stress markers in schizophrenia," *Science China Life Sciences*, vol. 53, no. 1, pp. 112–124, 2010.

[97] O. Akyol, S. Zoroglu, F. Armutcu, S. Sahin, and A. Gurel, "Nitric oxide as a physiopathological factor in neuropsychiatric disorders," *In vivo*, vol. 18, no. 3, pp. 377–390, 2004.

[98] C. A. Doyle and P. Slater, "Application of [^{3}H] l-N^G-nitroarginine labelling to measure cerebellar nitric oxide synthase in patients with schizophrenia," *Neuroscience Letters*, vol. 202, no. 1-2, pp. 49–52, 1995.

[99] S. Bhattacharjee and W. J. Lukiw, "Alzheimer's disease and the microbiome," *Frontiers in Cellular Neuroscience*, vol. 7, pp. 1–4, 2013.

[100] H. Baba, T. Suzuki, H. Arai, and P. C. Emson, "Expression of nNOS and soluble guanylate cyclase in schizophrenic brain," *Neuroreport*, vol. 15, no. 4, pp. 677–680, 2004.

[101] H.-G. Bernstein, A. Stanarius, B. Baumann et al., "Nitric oxide synthase-containing neurons in the human hypothalamus: reduced number of immunoreactive cells in the paraventricular nucleus of depressive patients and schizophrenics," *Neuroscience*, vol. 83, no. 3, pp. 867–875, 1998.

[102] M. C. M. Ryan, N. Sharifi, R. Condren, and J. H. Thakore, "Evidence of basal pituitary–adrenal overactivity in first episode, drug naïve patients with schizophrenia," *Psychoneuroendocrinology*, vol. 29, no. 8, pp. 1065–1070, 2004.

[103] J. P. Maia-de-Oliveira, C. Trzesniak, I. R. Oliveira et al., "Nitric oxide plasma/serum levels in patients with schizophrenia: a systematic review and meta-analysis," *Revista Brasileira de Psiquiatria*, vol. 34, pp. 149–162, 2012.

[104] K. Tanda, A. Nishi, N. Matsuo et al., "Abnormal social behavior, hyperactivity, impaired remote spatial memory, and increased D1-mediated dopaminergic signaling in neuronal nitric oxide synthase knockout mice," *Molecular Brain*, vol. 2, no. 1, p. 19, 2009.

[105] C. R. Sunico, F. Portillo, D. González-Forero, and B. Moreno-López, "Nitric oxide-directed synaptic remodeling in the adult mammal CNS," *Journal of Neuroscience*, vol. 25, no. 6, pp. 1448–1458, 2005.

[106] X. R. Zhang, Y. X. Wang, Z. J. Zhang, L. Li, and G. P. Reynolds, "The effect of chronic antipsychotic drug on hypothalamic expression of neural nitric oxide synthase and dopamine D2 receptor in the male rat," *PLoS One*, vol. 7, no. 4, article e33247, 2012.

[107] Y.-S. Lau, E. Petroske, G. E. Meredith, and J. Q. Wang, "Elevated neuronal nitric oxide synthase expression in chronic haloperidol-treated rats," *Neuropharmacology*, vol. 45, no. 7, pp. 986–994, 2003.

[108] F. I. Tarazi, K. Zhang, and R. J. Baldessarini, "Long-term effects of newer antipsychotic drugs on neuronal nitric oxide synthase in rat brain," *Nitric Oxide*, vol. 7, no. 4, pp. 297–300, 2002.

[109] B. M. M. Ribeiro, M. R. S. do Carmo, R. S. Freire et al., "Evidences for a progressive microglial activation and increase in iNOS expression in rats submitted to a neurodevelopmental model of schizophrenia: reversal by clozapine," *Schizophrenia Research*, vol. 151, no. 1–3, pp. 12–19, 2013.

[110] H. B. Chen, W. N. Wu, W. Wang et al., "Cystathionine-β-synthase-derived hydrogen sulfide is required for amygdalar long-term potentiation and cued fear memory in rats," *Pharmacology Biochemistry and Behavior*, vol. 155, pp. 16–23, 2017.

[111] J. F. Trentini, J. T. O'Neill, S. Poluch, and S. L. Juliano, "Prenatal carbon monoxide impairs migration of interneurons into the cerebral cortex," *Neurotoxicology*, vol. 53, pp. 31–44, 2016.

[112] S. Prabakaran, J. E. Swatton, M. M. Ryan et al., "Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress," *Molecular Psychiatry*, vol. 9, no. 7, pp. 684–697, 2004.

[113] X.-Q. Song, L.-X. Lv, W.-Q. Li, Y.-H. Hao, and J.-P. Zhao, "The interaction of nuclear factor-kappa B and cytokines is associated with schizophrenia," *Biological Psychiatry*, vol. 65, no. 6, pp. 481–488, 2009.

[114] C. J. L. Murray and A. D. Lopez, "Evidence-based health policy–lessons from the global burden of disease study," *Science*, vol. 274, no. 5288, pp. 740–743, 1996.

[115] R. T. de Sousa, M. V. Zanetti, G. F. Busatto et al., "Lithium increases nitric oxide levels in subjects with bipolar disorder during depressive episodes," *Journal of Psychiatric Research*, vol. 55, pp. 96–100, 2014.

[116] A. C. Andreazza, M. Kauer-Sant'Anna, B. N. Frey et al., "Oxidative stress markers in bipolar disorder: a meta-analysis," *Journal of Affective Disorders*, vol. 111, no. 2-3, pp. 135–144, 2008.

[117] S. Selek, H. A. Savas, H. S. Gergerlioglu, F. Bulbul, E. Uz, and M. Yumru, "The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode," *Journal of Affective Disorders*, vol. 107, no. 1–3, pp. 89–94, 2008.

[118] C. L. M. Bon and J. Garthwaite, "On the role of nitric oxide in hippocampal long-term potentiation," *Journal of Neuroscience*, vol. 23, no. 5, pp. 1941–1948, 2003.

[119] L. Liu and J. S. Stamler, "NO: an inhibitor of cell death," *Cell Death & Differentiation*, vol. 6, no. 10, pp. 937–942, 1999.

[120] A. Riccio, R. S. Alvania, B. E. Lonze et al., "A nitric oxide signaling pathway controls CREB-mediated gene expression in neurons," *Molecular Cell*, vol. 21, no. 2, pp. 283–294, 2006.

[121] O. Sergent, B. Griffon, I. Morel et al., "Effect of nitric oxide on iron-mediated oxidative stress in primary rat hepatocyte culture," *Hepatology*, vol. 25, no. 1, pp. 122–127, 1997.

[122] R. T. de Sousa, M. T. van de Bilt, B. S. Diniz et al., "Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study," *Neuroscience Letters*, vol. 494, no. 1, pp. 54–56, 2011.

[123] T. Bschor and M. Bauer, "Efficacy and mechanisms of action of lithium augmentation in refractory major depression," *Current Pharmaceutical Design*, vol. 12, no. 23, pp. 2985–2992, 2006.

[124] M. Ghasemi and A. R. Dehpour, "The NMDA receptor/nitric oxide pathway: a target for the therapeutic and toxic effects of lithium," *Trends in Pharmacological Sciences*, vol. 32, no. 7, pp. 420–434, 2011.

[125] D. L. Feinstein, "Potentiation of astroglial nitric oxide synthase type-2 expression by lithium chloride," *Journal of Neurochemistry*, vol. 71, no. 2, pp. 883–886, 1998.

[126] H. Anai, Y. Ueta, R. Serino, M. Nomura, Y. Nakashima, and H. Yamashita, "Activation of hypothalamic neuronal nitric oxide synthase in lithium-induced diabetes insipidus rats," *Psychoneuroendocrinology*, vol. 26, no. 2, pp. 109–120, 2001.

[127] G. Bagetta, M. T. Corasaniti, G. Melino, A. M. Paoletti, A. Finazziagro, and G. Nistico, "Lithium and tacrine increase the expression of nitric oxide synthase mRNA in the hippocampus of rat," *Biochemical and Biophysical Research Communications*, vol. 197, no. 3, pp. 1132–1139, 1993.

[128] B. H. Harvey, M. E. Carstens, and J. J. F. Taljaard, "Evidence that lithium induces a glutamatergic: nitric oxide-mediated response in rat brain," *Neurochemical Research*, vol. 19, no. 4, pp. 469–474, 1994.

[129] P. Bhalla, N. Singla, and D. K. Dhawan, "Potential of lithium to reduce aluminium-induced cytotoxic effects in rat brain," *Biometals*, vol. 23, no. 2, pp. 197–206, 2010.

[130] H. A. Savas, H. S. Gergerlioglu, F. Armutcu et al., "Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: impact of past episodes," *The World Journal of Biological Psychiatry*, vol. 7, no. 1, pp. 51–55, 2006.

[131] M. Van Spronsen and C. C. Hoogenraad, "Synapse pathology in psychiatric and neurologic disease," *Current Neurology and Neuroscience Reports*, vol. 10, no. 3, pp. 207–214, 2010.

[132] J. E. Kang, M. M. Lim, R. J. Bateman et al., "Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle," *Science*, vol. 326, no. 5955, pp. 1005–1007, 2009.

[133] G. Scapagnini, V. D'Agata, V. Calabrese et al., "Gene expression profiles of heme oxygenase isoforms in the rat brain," *Brain Research*, vol. 954, no. 1, pp. 51–59, 2002.

[134] D. E. Barañano and S. H. Snyder, "Neural roles for heme oxygenase: contrasts to nitric oxide synthase," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 20, pp. 10996–11002, 2001.

[135] H. M. Schipper and W. Song, "A heme oxygenase-1 transducer model of degenerative and developmental brain disorders," *International Journal of Molecular Sciences*, vol. 16, no. 12, pp. 5400–5419, 2015.

[136] W. Hirose, K. Ikematsu, and R. Tsuda, "Age-associated increases in heme oxygenase-1 and ferritin immunoreactivity in the autopsied brain," *Legal Medicine*, vol. 5, pp. S360–S366, 2003.

[137] W. Song, H. Zukor, A. Liberman et al., "Astroglial heme oxygenase-1 and the origin of corpora amylacea in aging and degenerating neural tissues," *Experimental Neurology*, vol. 254, pp. 78–89, 2014.

[138] H. M. Schipper, W. Song, H. Zukor, J. R. Hascalovici, and D. Zeligman, "Heme oxygenase-1 and neurodegeneration: expanding frontiers of engagement," *Journal of Neurochemistry*, vol. 110, no. 2, pp. 469–485, 2009.

[139] R. Nisticò, V. Cavallucci, S. Piccinin et al., "Insulin receptor β-subunit haploinsufficiency impairs hippocampal late-phase LTP and recognition memory," *Neuromolecular Medicine*, vol. 14, no. 4, pp. 262–269, 2012.

[140] J. Garthwaite, "Concepts of neural nitric oxide-mediated transmission," *European Journal of Neuroscience*, vol. 27, no. 11, pp. 2783–2802, 2008.

[141] Q.-F. Zhao, J.-T. Yu, and L. Tan, "S-Nitrosylation in Alzheimer's disease," *Molecular Neurobiology*, vol. 51, no. 1, pp. 268–280, 2015.

[142] D. M. Wilcock, M. R. Lewis, W. E. van Nostrand et al., "Progression of amyloid pathology to Alzheimer's disease pathology in an amyloid precursor protein transgenic mouse model by removal of nitric oxide synthase 2," *Journal of Neuroscience*, vol. 28, no. 7, pp. 1537–1545, 2008.

[143] I. Goussakov, M. B. Miller, and G. E. Stutzmann, "NMDA-mediated Ca^{2+} influx drives aberrant ryanodine receptor activation in dendrites of young Alzheimer's disease mice," *Journal of Neuroscience*, vol. 30, no. 36, pp. 12128–12137, 2010.

[144] D. Shilling, M. Muller, H. Takano et al., "Suppression of InsP3 receptor-mediated Ca^{2+} signaling alleviates mutant presenilin-linked familial Alzheimer's disease pathogenesis," *Journal of Neuroscience*, vol. 34, no. 20, pp. 6910–6923, 2014.

[145] S. Chakroborty and G. E. Stutzmann, "Early calcium dysregulation in Alzheimer's disease: setting the stage for synaptic dysfunction," *Science China Life Sciences*, vol. 54, no. 8, pp. 752–762, 2011.

[146] S. Chakroborty, J. Kim, C. Schneider, A. R. West, and G. E. Stutzmann, "Nitric oxide signaling is recruited as a compensatory mechanism for sustaining synaptic plasticity in Alzheimer's disease mice," *Journal of Neuroscience*, vol. 35, no. 17, pp. 6893–6902, 2015.

[147] Z. J. Palmer, R. R. Duncan, J. R. Johnson et al., "S-Nitrosylation of syntaxin 1 at Cys145 is a regulatory switch controlling Munc18-1 binding," *Biochemical Journal*, vol. 413, no. 3, pp. 479–491, 2008.

[148] A. Ratnayaka, V. Marra, D. Bush, J. J. Burden, T. Branco, and K. Staras, "Recruitment of resting vesicles into recycling pools supports NMDA receptor-dependent synaptic potentiation in cultured hippocampal neurons," *The Journal of Physiology*, vol. 590, no. 7, pp. 1585–1597, 2012.

Hindawi
Neural Plasticity
Volume 2018, Article ID 9275239, 9 pages
https://doi.org/10.1155/2018/9275239

Research Article

Cardiac Arrest Induces Ischemic Long-Term Potentiation of Hippocampal CA1 Neurons That Occludes Physiological Long-Term Potentiation

James E. Orfila,[1] Nicole McKinnon,[2] Myriam Moreno,[1] Guiying Deng,[3] Nicholas Chalmers,[1] Robert M. Dietz,[2] Paco S. Herson,[1,3] and Nidia Quillinan[1]

[1]*Neuronal Injury Program, Department of Anesthesiology, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA*
[2]*Department of Pediatrics, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA*
[3]*Department of Pharmacology, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA*

Correspondence should be addressed to Nidia Quillinan; nidia.quillinan@ucdenver.edu

Received 27 November 2017; Revised 15 March 2018; Accepted 5 April 2018; Published 26 April 2018

Academic Editor: Paola Bonsi

Ischemic long-term potentiation (iLTP) is a form of synaptic plasticity that occurs in acute brain slices following oxygen-glucose deprivation. *In vitro*, iLTP can occlude physiological LTP (pLTP) through saturation of plasticity mechanisms. We used our murine cardiac arrest and cardiopulmonary resuscitation (CA/CPR) model to produce global brain ischemia and assess whether iLTP is induced *in vivo*, contributing to the functionally relevant impairment of pLTP. Adult male mice were subjected to CA/CPR, and slice electrophysiology was performed in the hippocampal CA1 region 7 or 30 days later. We observed increased miniature excitatory postsynaptic current amplitudes, suggesting a potentiation of postsynaptic AMPA receptor function after CA/CPR. We also observed increased phosphorylated GluR1 in the postsynaptic density of hippocampi after CA/CPR. These data support the *in vivo* induction of ischemia-induced plasticity. Application of a low-frequency stimulus (LFS) to CA1 inputs reduced excitatory postsynaptic potentials in slices from mice subjected to CA/CPR, while having no effects in sham controls. These results are consistent with a reversal, or depotentiation, of iLTP. Further, depotentiation with LFS partially restored induction of pLTP with theta burst stimulation. These data provide evidence for iLTP following *in vivo* ischemia, which occludes pLTP and likely contributes to network disruptions that underlie memory impairments.

1. Introduction

Ischemic long-term potentiation (iLTP) is an increase in excitatory synaptic strength that occurs immediately following oxygen and glucose deprivation (OGD) in acute brain slices [1–6]. Elevations in extracellular glutamate during OGD cause prolonged activation of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) receptors, resulting in an influx of sodium and calcium. Rises in intracellular calcium stimulate calcium/calmodulin-dependent protein kinase (CAMKII) signaling, which potentiates postsynaptic excitatory function via increased AMPA receptor phosphorylation and expression at the synapse. There is some indirect evidence to support that iLTP occurs following *in vivo* ischemia. Previously, we demonstrated increased activation of CAMKII within hours of global ischemia induced by cardiac arrest [7]. There is also evidence to support acute activation of CAMKII and increased NMDA receptor expression in the hippocampus within hours of *in vivo* focal ischemia [8]. However, it is unknown whether acute activation of CAMKII seen following *in vivo* ischemia causes synaptic potentiation in the hippocampus or whether ischemic LTP is maintained for days beyond the ischemic event.

Shared mechanisms between ischemic and physiologic LTP suggest that it is likely these plasticity processes would occlude one another, as has been described in studies where acute hippocampal brain slices were subjected to *in vitro*

ischemia [3, 4]. Physiological hippocampal long-term potentiation (pLTP) is an experience- or frequency-dependent increase in synaptic strength and is a cellular substrate for learning and memory. Similar to iLTP, pLTP occurs through an NMDA and CAMKII-dependent increase in synaptic AMPA receptor function [9–12]. Memory deficits in cardiac arrest survivors are attributed to ischemic injury to the hippocampus that causes loss of pyramidal CA1 neurons [13, 14]. In addition to neuronal cell death, global ischemia causes persistent deficits in pLTP in surviving neurons of the CA1 [7, 15–19]. Therefore, pLTP deficits caused by brain ischemia likely contribute to memory deficits, and therapies that restore pLTP have the potential to improve cognitive function after CA/CPR. Acute neuroprotective interventions that reduce CA1 injury can also prevent pLTP deficits; however, there is no strategy that targets LTP deficits at delayed time points and that is independent of preventing neuronal cell death [7, 15, 19, 20]. The goal of this study was to determine whether *in vivo* global ischemia from cardiac arrest causes ischemic LTP that prevents physiological LTP.

2. Methods

2.1. Experimental Animals and Cardiac Arrest Model. The Institutional Animal Care and Use Committee (IACUC) at the University of Colorado approved all experimental protocols in accordance with the National Institutes of Health and guidelines for the care and use of animals in research. Analysis was performed with investigators blinded to experimental groups. Adult (8–12-week-old) male C57Bl6 (Charles River, Wilmington, MA) mice were subjected to CA/CPR as previously described during the ON light cycle [21–23]. A total of 54 animals were included in this study.

Briefly, anesthesia was induced with 3% isoflurane and maintained with 1.5–2% isoflurane in oxygen-enriched air using a nose cone. Temperature probes were inserted in the left ear and rectum to monitor tympanic (head) and body temperature simultaneously. A PE-10 catheter was inserted into the right internal jugular vein for drug administration. Needle electrodes were placed subcutaneously on the chest for continuous electrocardiogram (EKG) monitoring. Animals were endotracheally intubated and connected to a mouse ventilator (MiniVent Ventilator, Harvard Apparatus). Cardiac arrest was induced with injection of 50 μl KCl (0.5 M) via the jugular catheter and confirmed by asystole on EKG. During cardiac arrest, the endotracheal tube was disconnected, anesthesia stopped, and body temperature was allowed to spontaneously decrease to a minimum of 35.5°C, and head temperature was maintained at 37.5°C. Resuscitation began eight minutes after induction of cardiac arrest by slow injection of 0.5–1.0 ml epinephrine solution (16 μg epinephrine/ml 0.9% saline), chest compressions, and ventilation with 100% oxygen at a respiratory rate of 200 breaths/min. Chest compressions were stopped as soon as spontaneous circulation was restored. Resuscitation was abandoned if spontaneous circulation was not restored within 2.5 minutes. Mice were extubated after they recovered an adequate respiratory rate and effort. Sham controls underwent the same procedures as mice undergoing cardiac arrest including anesthesia, intubation, placement of the jugular catheter, EKG leads, and temperature management. Sham controls did not receive KCl or epinephrine injections or chest compressions. The animals were placed in a single-housed static recovery cage on a heated water blanket (35°C) for the first 24 hours of recovery and at ambient room temperature for long-term recovery (up to 30 days). Mice received soft food and subcutaneous saline for 3 days after surgery and had free access to water and regular chow.

2.2. Acute Slice Preparation. Following CA/CPR or sham surgery, mice were anesthetized with isoflurane (3.5%) and transcardially perfused with ice-cold artificial cerebral spinal fluid (ACSF) containing (in mmol/l) 126 NaCl, 2.5 KCl, 2.5 $CaCl_2$, 1.2 $MgCl_2$, 1.2 NaH_2PO_4, 21.4 $NaHCO_3$, and 11 D-glucose, bubbled with 95% O_2/5% CO_2 to maintain pH of 7.4. Mice were decapitated and brains were rapidly removed. Horizontal hippocampal sections (300 μM) were cut in ice-cold ACSF using a VT1200S Vibratome (Leica, Buffalo Grove, IL, USA) and then maintained at room temperature for at least 30 minutes prior to recording.

2.3. Miniature Excitatory Postsynaptic Currents (mEPSCs). Whole-cell recordings were performed at room temperature (22°C) in a submersion chamber and were continuously perfused with ACSF containing picrotoxin (PTX, 100 μM) and tetrodotoxin (TTX, 250 nM). Recordings were obtained using borosilicate glass pipettes that were fabricated using a Flaming/Brown heat puller (Sutter Instruments, Novato, CA, USA) to a resistance of 2–4 MΩ. Internal recording solution contained (in mmol/l) 120 K-gluconate, 9 KCl, 10 KOH, 4 NaCl, 10 HEPES, 0.05 EGTA, 1 $MgCl_2$, 4 Na_2ATP, and 0.4 Na_2GTP. Series resistance was <20 MΩ and did not change more than 20% during the experiment. Whole-cell voltage-clamp recordings were performed at a holding potential of −70 mV. Gap-free continuous recordings were acquired in 3-minute sweeps. Miniature events were identified using Clampfit software with template event detection, and mEPSC amplitude and frequency were quantified for each cell. To generate cumulative probability histograms events from all sham or CA/CPR, mice were pooled.

2.4. Extracellular Field Recording. For extracellular recordings, slices were transferred to an interface recording chamber that was continuously perfused with ACSF (1.5 ml/min) and warmed to 32°C. Extracellular field excitatory postsynaptic potentials (fEPSPs) recorded in the stratum radiatum were evoked with a bipolar stimulus electrode positioned in the stratum moleculare/luminaris to evoke glutamate release from Schaffer collaterals (0.05 Hz). Input-output curves were generated by increasing stimulus intensity in 10 μA increments and recording fEPSP slopes. Stimulus intensity was adjusted to produce a fEPSP with a slope that was 50% of the maximum. A stable baseline fEPSP was recorded for 20 minutes before theta burst stimulation (TBS; 10 trains of 4–100 Hz pulses) was applied to Schaffer collaterals. fEPSPs were recorded for 60 minutes following TBS, and percent change from baseline was calculated for

the last 10 minutes of the recording. Low-frequency stimulation (LFS) was delivered for 10 minutes (900 pulses at 0.5 Hz), and percent change from baseline was analyzed 20 minutes after LFS. Data were compressed to 1-minute averages, and the extent of LTP or depotentiation was measured as percentage of the baseline fEPSP slope during the last 10 minutes of the recording.

2.5. Western Blot Analysis. Following CA/CPR or sham surgery, mice were deeply anesthetized with isoflurane (3.5%), heads were decapitated and brains were rapidly removed. Hippocampi were isolated and rapidly frozen with 2-methylbutane on dry ice. Individual hippocampi were homogenized in sucrose buffer containing protease and phosphatase inhibitors using a PTFE tissue grinder in a glass tube. Homogenates were centrifuged at 1000 ×g for 10 minutes to remove cellular debris and nuclei. Supernatant was removed and spun at 10,000 ×g for 15 minutes. This supernatant was collected and spun at 100,000 ×g for 60 minutes, yielding a supernatant that contains the cytosolic cellular fraction (S3). The pellet (P2) was resuspended in triton buffer and then centrifuged at 32,000 ×g for 20 minutes, yielding a pellet (P4) that contains the postsynaptic density (PSD) fraction. This pellet was resuspended in N-PER buffer (Thermo Fisher, Waltham, MA) containing protease and phosphatase inhibitors. The PSD protein concentration was quantified using a BCA kit, and samples were diluted in 4x denaturing sample buffer to a final concentration of 1 μg/μl. Protein (20 μg) was loaded onto a polyacrylamide gel for protein electrophoresis and transferred to a PVDF membrane. Membranes were blocked in Tris-buffered saline with Tween (TBS-T) containing 5% BSA or milk. Primary antibody incubations were performed overnight at 4°C and detected using horseradish peroxidase-conjugated secondary antibodies. Bands were visualized using a maximum sensitivity-enhanced chemiluminescence substrate with the ChemiDoc Gel Imaging System (Bio-Rad, Hercules, CA). Multiple antibodies were probed on each membrane by stripping with Restore Plus stripping buffer after chemiluminescent detection. Integrated volume of bands was normalized to beta-actin integrated volume for that sample. Normalized protein expression is presented relative to sham controls.

2.6. Statistics. For electrophysiology experiments, n indicates the number of recordings with no more than two recordings for a given experiment from a single animal. Data are presented as mean ± SEM. Statistical comparisons were made between two groups using Student's t-test and multiple groups using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc comparison of groups relative to control. Statistical comparisons were performed using GraphPad Prism 7.0. Differences with a p value of <0.05 were considered significant.

3. Results

3.1. Increased AMPA Receptor Function following In Vivo Ischemia. The expression of LTP occurs through an increase in AMPA receptor function resulting from phosphorylation and increased synaptic expression. To directly measure postsynaptic AMPA receptor function, we performed whole-cell recording of miniature EPSCs (mEPSCs) in CA1 neurons 7 days after CA/CPR. Delayed neuronal cell death occurs at 2-3 days postinjury; therefore, by 7 days postinjury, cell death processes are complete and electrophysiology can be performed in surviving neurons that exhibit LTP deficits [7, 19, 22, 24]. Miniature excitatory events were isolated using tetrodotoxin (TTX, 250 nM) and picrotoxin (PTX, 100 μM) (Figure 1(a)). Mean mEPSC amplitude, kinetics, and frequency were analyzed using Clampfit template event detection. Cumulative frequency distributions of mEPSC amplitudes were generated by pooling events from recordings in sham (n = 2,729 events) and CA/CPR (n = 3,213 events). The cumulative frequency curve was right-shifted in mice after CA/CPR compared to sham controls, with larger maximum amplitudes (110.7 pA versus 56.2 pA) (Figure 1(b)). The shift to larger events was also detected as an increase in the mean mEPSC amplitude from 16.43 ± 0.94 ($n = 12$) to 20.74 ± 1.1 ($n = 15$; $p = 0.008$) (Figure 1(c)). Rise and decay kinetics of mEPSCs were not different between shams and controls (Table 1). There were also no changes in the biophysical properties of neurons that would account for the larger amplitude mEPSCs observed after CA/CPR (Table 1). Event frequency was similar in sham (1.4 ± 0.4, $n = 12$) and cardiac arrest mice (1.4 ± 0.3, $n = 15$; $p = 0.95$) (Figure 1(d)), indicating no change in synapse number. These data suggest there is increased postsynaptic AMPA receptor function at CA1 synapses following CA/CPR.

Synaptic potentiation results from NMDA receptor-dependent activation of CAMKII and the subsequent increase in AMPA receptor phosphorylation and expression at postsynaptic sites. Previously, we reported an acute increase in CAMKII activity (T286 phosphorylation) in the hippocampus 3-hour post-CA/CPR, suggesting an ischemia-induced increase in CAMKII activation [7]. To determine whether there are changes in glutamate receptor phosphorylation and expression at delayed time points after cardiac arrest, we isolated the hippocampus from shams and 7 days after CA/CPR, and protein fractions enriched for postsynaptic densities were subjected to Western blot analysis (Figure 2(a)). We observed an increase in levels of phosphorylated AMPA receptors (GluR1 pS831) from 1.01 ± 0.03 ($n = 7$) in shams to 1.23 ± 0.1 ($n = 6$) at 7 days postinjury ($p = 0.047$), consistent with an increase in receptor function (Figure 2(b)). GluR1 AMPA receptor expression (sham: 1 ± 0.16, $n = 7$; CA/CPR: 1.28 ± 0.22, $n = 7$) and GluR2/3 expression (sham: 1 ± 0.2, $n = 5$; CA/CPR: 1.25 ± 0.16, $n = 4$) were not different after cardiac arrest ($p = 0.312$ and $p = 0.36$, resp.) (Figures 2(c) and 2(d)). Ischemic LTP caused by *in vitro* ischemia can increase NMDA expression [8]. We observed a small increase in NMDA receptor (GluN1) from 1 ± 0.14 ($n = 5$) to 1.38 ± 0.21 ($n = 4$) expression that was not significant ($p = 0.1675$) (Figure 2(e)). Finally, we saw no change in PSD-95 levels after cardiac arrest (sham: 1 ± 0.1, $n = 7$; CA/CPR: 1.05 ± 0.21, $n = 7$; $p = 0.823$), suggesting no changes in the overall synapse density (Figure 2(f)). These data are consistent with our mEPSC data

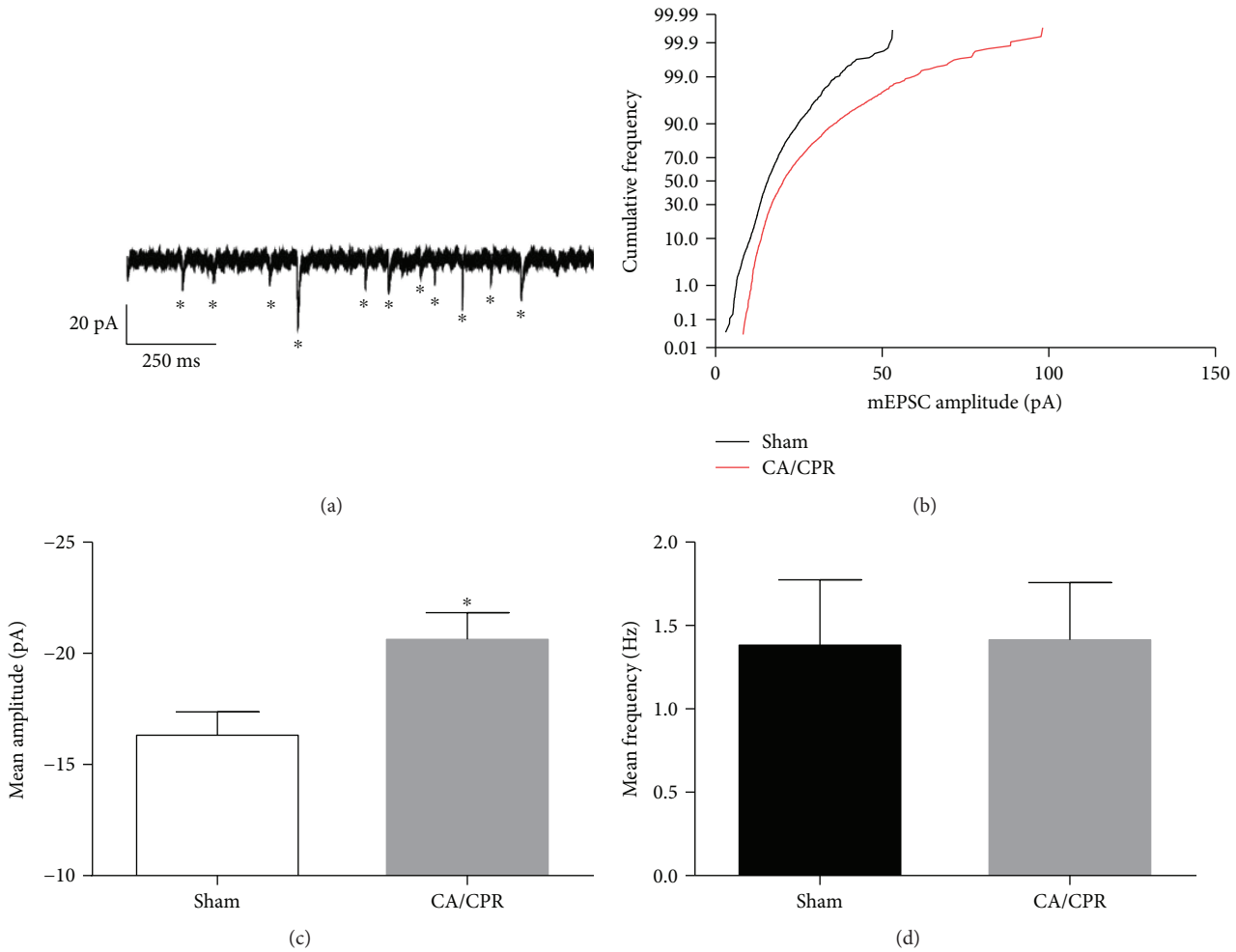


Figure 1: Lasting potentiation of miniature excitatory postsynaptic currents (mEPSCs) induced by cardiac arrest. (a) A representative trace from a sham control of whole-cell voltage clamp recording of mEPSC events recorded from CA1 neurons in acute brain slices. Events were detected with Clampfit software and are indicated with an asterisk. (b) CA/CPR produced a rightward shift in the cumulative frequency distribution of mEPSC amplitudes relative to shams. Events from sham (black, $n = 2729$ events) or CA/CPR (red, $n = 3213$ events) mice were pooled to generate histograms. (c) CA/CPR produced an increase in mean mEPSC amplitudes compared to sham. Mean mEPSC amplitude was calculated for each recording (sham: $n = 12$; CA/CPR: $n = 15$), and means for groups were compared using Student's unpaired t-test ($*$ indicates $p < 0.05$). (d) CA/CPR did not alter synaptic density in CA1 neurons. No change in mean mEPSC frequency was observed between sham and CA/CPR mice. Mean mEPSC frequency was calculated for each recording (sham: $n = 12$; CA/CPR: $n = 15$), and means for groups were compared using Student's unpaired t-test.

Table 1

	Sham	7 days	30 days	p value
R_m (MW)	281.0 ± 30.85 ($n = 10$)	230.6 ± 38.65 ($n = 16$)		0.367
C_m (pF)	5.738 ± 1.360 ($n = 10$)	9.224 ± 1.845 ($n = 16$)		0.1893
PPR (pulse 1/pulse 2)	1.32 ± 0.1 ($n = 5$)	1.30 ± 0.08 ($n = 8$)	1.33 ± 0.07 ($n = 4$)	0.889
I/O (slope)	3.65 ± 0.59 ($n = 6$)	4.57 ± 0.33 ($n = 6$)	3.85 ± 0.78 ($n = 6$)	0.548
EPSC rise time (ms)	2.68 ± 0.27 ($n = 12$)	2.37 ± 0.17 ($n = 15$)		0.3271
EPSC decay time (ms)	11.60 ± 1.08 ($n = 12$)	12.55 ± 0.99 ($n = 15$)		0.5273

showing increased amplitude and no change in frequency of mEPSC events.

3.2. Depotentiation Restores the Ability to Induce Physiological LTP in Postischemic Neurons. Depotentiation, which is the reversal of LTP, is induced with low-frequency stimulation of synapses that were previously given high-frequency stimulation to induce LTP [25–28]. We hypothesized that ischemic LTP following CA/CPR would be reversed with a depotentiation stimulus.

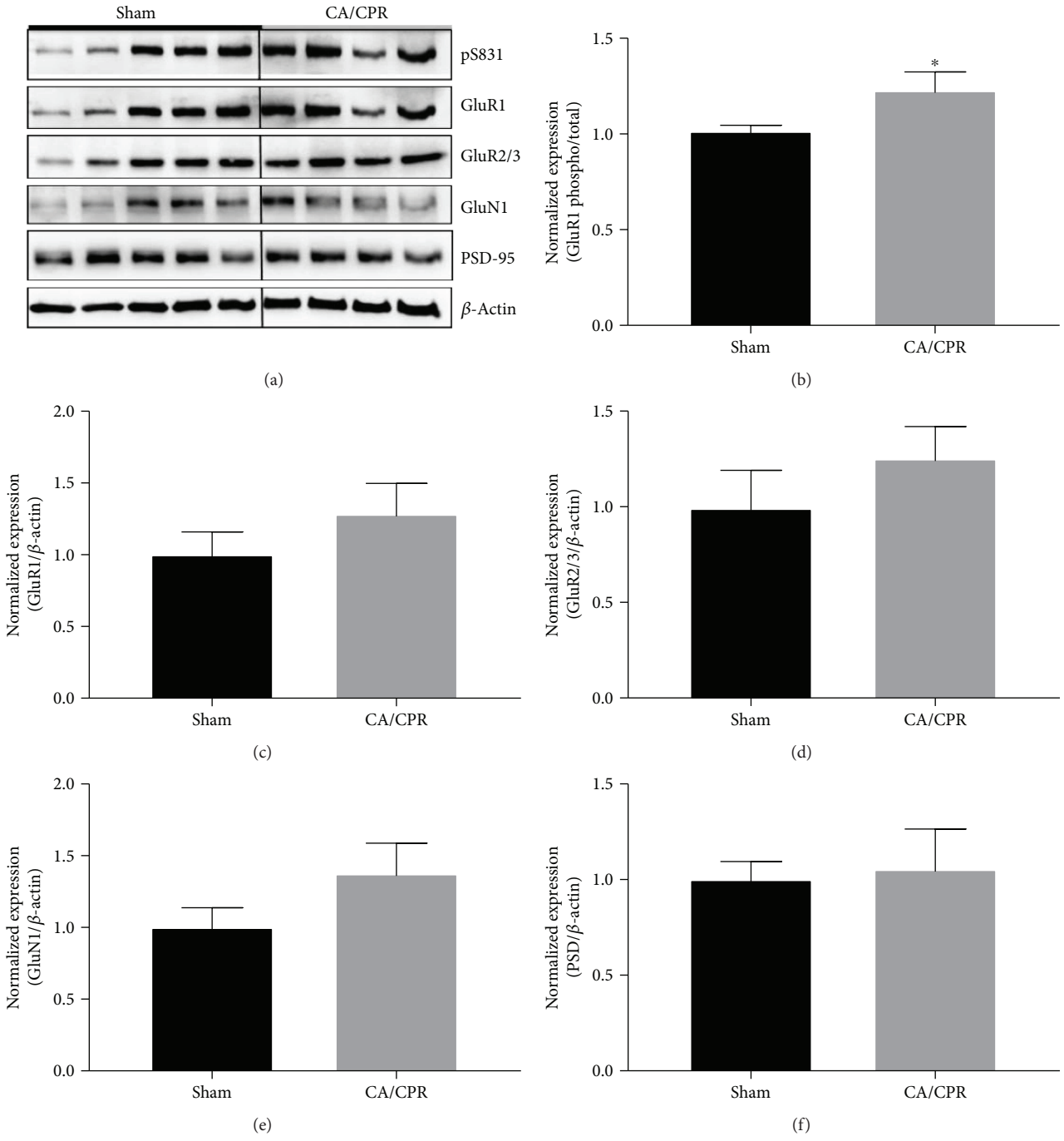


Figure 2: Increased AMPA receptor phosphorylation after CA/CPR. (a) Representative blots of protein expression from synaptic fractions of sham and CA/CPR hippocampus. Blots were cropped to show bands at molecular weight for indicated proteins. (b) Normalized phosphorylated S831: total GluR1 expression was calculated for each sample by dividing optical density of phosphoS831 by total GluR1 density within the same blot. (c) Normalized GluR1 expression was calculated for each sample by dividing optical density of total GluR1 by β-actin density within the same blot. (d) Normalized GluR2/3 expression was calculated for each sample by dividing optical density of total GluR2/3 by β-actin density within the same blot. (e) Normalized GluN1 expression was calculated for each sample by dividing optical density of total GluN1 by β-actin density within the same blot. (f) Normalized PSD-95 expression was calculated for each sample by dividing optical density of PSD-95 by β-actin density within the same blot. Values were normalized to sham controls. Shams ($n = 7$) and CA/CPR ($n = 6$) groups were compared using Student's t-test. $*$ indicates $p < 0.05$.

Previous studies use stimulation frequencies ranging between 0.5 and 2 Hz to depotentiate pLTP without inducing long-term depression (LTD). We found that 900 pulses, delivered at 0.5 Hz, reversed LTP that was induced by a previous theta burst stimulation (TBS) from $182.5 \pm 7.7\%$ to $132.7 \pm 15.4\%$ of baseline amplitude ($n = 5$). Importantly, this LFS protocol did not induce LTD in naive controls, having no effect on fEPSP slope

from baseline following LFS ($n = 6$; $p = 0.13$) (Figure 3(a)), thus fitting the definition of a depotentiation protocol.

We next tested whether a depotentiation LFS protocol was capable of reducing synaptic strength in mice subjected to CA/CPR, thus providing further evidence of sustained iLTP. In sham controls, fEPSP slopes were $110 \pm 4.2\%$ ($n = 6$) of baseline after LFS, an increase that was not statistically significant ($p = 0.06$) (Figure 3(b)). Acute slices prepared 7 days after CA/CPR showed a decrease in fEPSP slope to $83 \pm 10.6\%$ ($n = 7$) of baseline after LFS, a change that was not statistically different from baseline ($p = 0.2$) but was significantly different than the change observed in controls ($p = 0.007$). At 30 days after CA/CPR, the change in fEPSP slope to $75.73 \pm 7.0\%$ ($n = 5$) of baseline after LFS was significantly different from baseline ($p = 0.015$) and from the change observed in controls ($p = 0.002$). This provides additional evidence for CA1 synapses being in a potentiated state following *in vivo* ischemia.

The induction of ischemic LTP by CA/CPR may occlude physiological LTP. To test this, we delivered LFS to induce depotentiation and followed this with TBS in slices from mice at 7 days postinjury. After acquiring a stable 10-minute baseline, we delivered LFS, resulting in a decrease of fEPSP slope to $87.7 \pm 0.4\%$ ($n = 5$) of baseline (Figure 3(c), dotted line). After 20 minutes, we delivered TBS, which increased fEPSP slope to $115.1 \pm 6.1\%$ of original baseline, a potentiation of 28% ($p = 0.015$) (Figure 3(c), shaded blue). These data suggest that LTP mechanisms are saturated, and that reversal of ischemic LTP with LFS partially restores the capacity to induce physiological LTP.

4. Discussion

We have provided several pieces of evidence for the presence of sustained ischemic LTP subsequent to *in vivo* global ischemia caused by cardiac arrest: (1) increased postsynaptic glutamate receptor function, (2) increased postsynaptic glutamate receptor phosphorylation, and (3) the ability to depotentiate CA1 synapses after cardiac arrest. Further, we have shown that ischemic LTP occludes physiological LTP, providing a possible target for interventional strategies to improve memory function after cardiac arrest.

To our knowledge, this is the first study to demonstrate that *in vivo* ischemia causes synaptic alterations that are consistent with ischemic LTP. Until now, all electrophysiological evidence for this phenomenon comes from *in vitro* studies using oxygen and glucose deprivation in slices. Therefore, by showing that this phenomenon occurs in vivo, we suggest that this is a mechanism through which memory impairment occurs. Ischemic LTP is similar to physiological LTP in its NMDA receptor dependence, activation of intracellular signaling, and an increase in postsynaptic AMPA receptor function [3, 5]. The stimulus for inducing ischemic LTP is the massive increase in extracellular glutamate that occurs within minutes of the onset of ischemia [29–33]. Importantly, it is this massive increase in extracellular glutamate that stimulates excitotoxic cell death. By enhancing postsynaptic responses to extracellular glutamate, ischemic LTP likely amplifies excitotoxicity mechanisms [34, 35], but it is unclear from *in vitro* studies what contribution this phenomenon has to CA1 injury after CA/CPR. Similarly, it is difficult to disentangle ischemic LTP and excitotoxicity *in vivo*, as they have similar induction mechanisms. Previous work from our laboratory and others has shown that pharmacological or genetic interventions reduce NMDA receptor activation or CAMKII activation, not only reducing neuronal cell death but also preserving physiological LTP [7, 19]. It is possible that neuroprotective strategies prevent LTP impairments, in part, by blocking ischemic LTP.

Our strongest evidence for ischemic LTP comes from electrophysiological recordings that demonstrate increased miniature EPSC amplitude. The advantage of this method is that we can specifically assess postsynaptic receptor function in CA1 region of the hippocampus. In our recording conditions, increased mEPSC amplitudes likely represent increased AMPA rather than NMDA receptor function. Other groups have reported that iLTP observed at acute time points is a result of increased expression and function of NMDA receptors [1, 3, 8]. However, we have previously demonstrated no change in NMDA receptor function or expression at 7 days after CA/CPR, consistent with our results here [19, 20]. These differences may be due to the use of *in vivo* versus *in vitro* models, or that our studies were performed days, rather than hours after the ischemic insult. Analysis of glutamate receptor expression performed here was from the synaptic fraction of the entire hippocampus, not just the CA1 region. Therefore, increases in CA1 receptor expression may be underrepresented within this pool. Regardless, our Western blot data provided evidence for increased phosphorylation of the GluR1 AMPA receptor subunit, which is consistent with our electrophysiological data. There have been mixed results as to whether iLTP has a presynaptic mechanism [3, 6]. We failed to detect differences in paired-pulse ratio, suggesting a postsynaptic mechanism for iLTP induced by CA/CPR. Others have reported that impaired hippocampal LTP following global ischemia is associated with reduced spine densities [36–38]. However, we did not detect a reduction in mEPSC frequency and PSD-95 expression, which are indirect measures of the number of synapses. Therefore, our data is consistent with ischemia-induced changes in plasticity without changes in the number of functional synapses. However, further experiments are needed to rule out an ischemia effect on spine density that may contribute to impaired synaptic plasticity.

Physiological LTP and ischemic LTP have shared mechanisms and, therefore, have the ability to occlude one another. Indeed, tetanic stimulation delivered just prior to OGD prevents ischemic LTP and vice versa [4–6]. Remarkably, we saw that depotentiation prior to theta burst stimulation allowed for the induction of physiological LTP. Therefore, these results support in vitro findings that ischemic LTP saturates plasticity mechanisms to occlude physiological LTP. The stimulus frequency used to depotentiate had no effect on naive control slices, giving us confidence that we induced the depotentiation of synapses, rather than inducing long-term depression, which has different signaling mechanisms. While there was some physiological LTP following depotentiation, LFS did not restore completely back

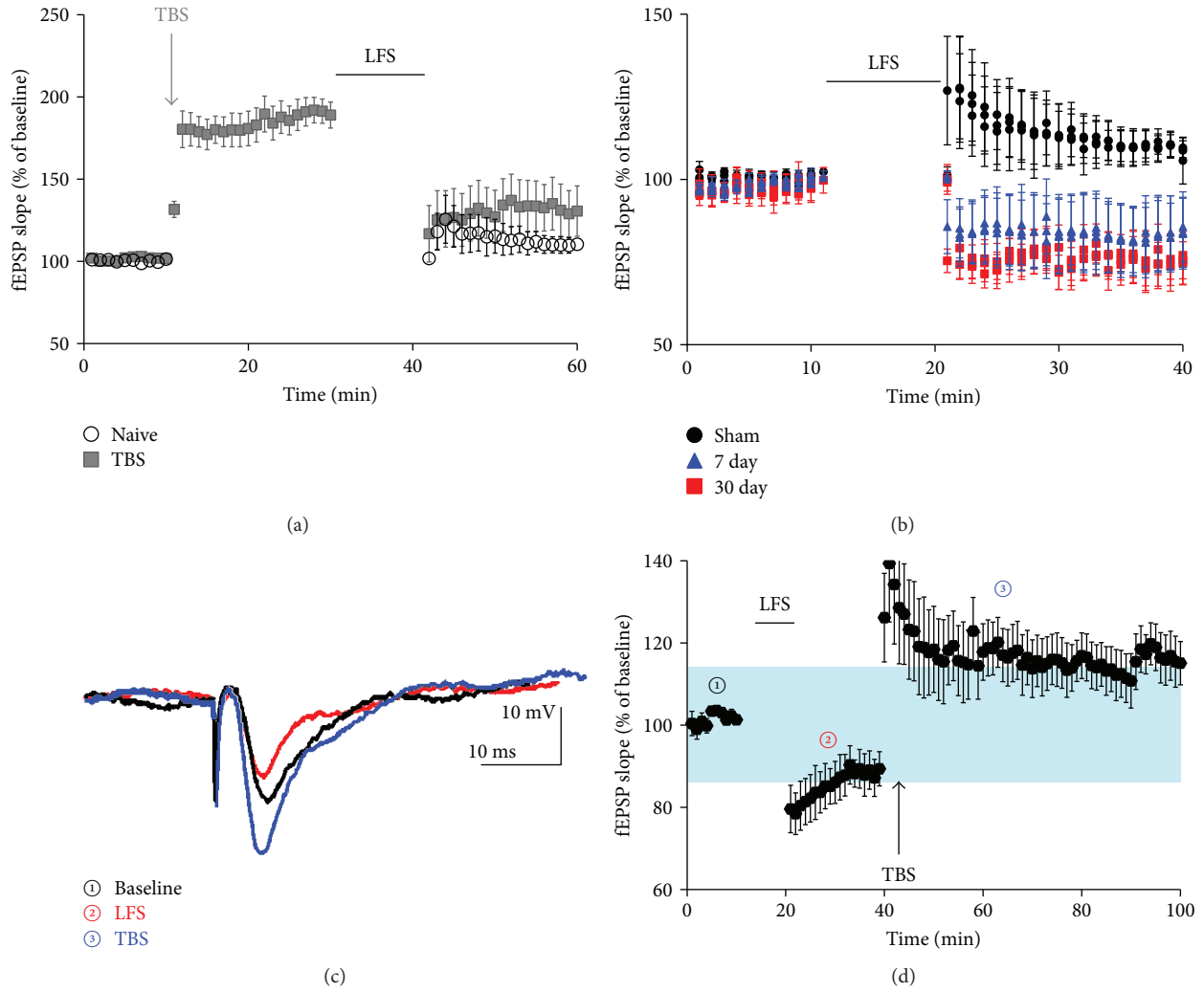


Figure 3: Depotentiation with low-frequency stimulation (LFS) reversed ischemic LTP and partially restored physiological LTP. (a) LFS depotentiates physiological LTP. 20 minutes after theta burst stimulation (TBS), LFS was delivered for 10 minutes (900 pulses at 0.5 Hz), resulting in a significant reduction in fEPSP slope (grey squares). LFS delivered to naive slices that did not receive TBS did not alter fEPSP slope (black circles). (b) LFS was delivered to slices from sham control (black circles) or 7 (blue triangles) or 30 days (red squares) after CA/CPR. LFS reduces fEPSC only in mice that were subjected to CA/CPR, indicating a reversal of iLTP. (c) Representative trace in recordings where we obtained a baseline (black trace) delivered LFS which reduced fEPSP amplitude (red trace) and subsequent TBS, which induced LTP (blue trace). (d) Summary of recordings in which we first delivered LFS then delivered TBS. Numbers on graph correlate with traces in panel (c). Magnitude of pLTP is shaded in blue.

to naive control levels. Therefore, it is likely that there are additional mechanisms that contribute to the LTP impairments in the hippocampus after cerebral ischemia. Regardless, these data suggest that induction of depotentiation to restore physiological plasticity may be a relevant therapy for improving memory function after ischemic brain injury. Future studies should address whether *in vivo* low-frequency electrical stimulation of the hippocampus, with implanted electrodes or through transmagnetic stimulation, can produce depotentiation and reduce memory deficits *in vivo*.

In vitro studies have been limited in their ability to record ischemic LTP for only the first hours after ischemia. Here, we are able to show that ischemic LTP is maintained for weeks after injury onset. At 7 and 30 days of postinjury, cell death mechanisms have subsided and recordings are from the surviving hippocampal network. Our ability to depotentiate ischemic LTP and then induce physiological LTP at these delayed time points demonstrates that LTP impairments can be targeted to improve synaptic function, independent of acute neuroprotection. This is an important advance, as acute neuroprotective strategies have failed to improve cognitive outcomes in clinical trials. Cognitive impairments are present in patients that receive therapeutic hypothermia, the only strategy that has given positive results in cardiac arrest victims [39–41]. Therefore, strategies that can provide additional benefit to therapeutic hypothermia have promised to improve neurological function and quality of life for patients. Interestingly, rodent studies have shown that exposure of animals to novel environments can depotentiate

previously acquired experience-dependent LTP, indicating the potential for novel rehabilitation strategies to reverse iLTP [28]. Future studies should determine whether such a behavioral paradigm could depotentiate ischemic LTP in the intact animal and improve future memory behavior.

In summary, we have demonstrated that *in vivo* global ischemia produces ischemic LTP which is the result of increased postsynaptic AMPA receptor function. Is iLTP beneficial or detrimental to hippocampal function? Our data demonstrating no change in input-output relations or synaptic density suggest that the hippocampal network is able to compensate for the loss of CA1 neurons after CA/CPR. Ischemic LTP may contribute to this normalization and therefore may have some benefit to the hippocampal network. However, the maintenance of iLTP for weeks after the ischemic insult is detrimental to physiological plasticity and likely worsens memory impairments. Thus, it appears that iLTP may serve as a beneficial compensatory mechanism following brain ischemia that if sustained during the chronic phase is detrimental to long-term recovery. Importantly, we show that this pathological form of plasticity is reversible and thus may be a therapeutic target for cognitive deficits after brain ischemia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by AHA BGIA25670032 (Nidia Quillinan) and R01 NS046072 (Nidia Quillinan) and NINDS R01 NS080851 (Paco S. Herson) and R01 NS092645 (Paco S. Herson).

References

[1] V. Crepel, C. Hammond, P. Chinestra, D. Diabira, and Y. Ben-Ari, "A selective LTP of NMDA receptor-mediated currents induced by anoxia in CA1 hippocampal neurons," *Journal of Neurophysiology*, vol. 70, no. 5, pp. 2045–2055, 1993.

[2] V. Crepel, C. Hammond, K. Krnjevic, P. Chinestra, and Y. Ben-Ari, "Anoxia-induced LTP of isolated NMDA receptor-mediated synaptic responses," *Journal of Neurophysiology*, vol. 69, no. 5, pp. 1774–1778, 1993.

[3] K. S. Hsu and C. C. Huang, "Characterization of the anoxia-induced long-term synaptic potentiation in area CA1 of the rat hippocampus," *British Journal of Pharmacology*, vol. 122, no. 4, pp. 671–681, 1997.

[4] M. Lyubkin, D. M. Durand, and M. A. Haxhiu, "Interaction between tetanus long-term potentiation and hypoxia-induced potentiation in the rat hippocampus," *Journal of Neurophysiology*, vol. 78, no. 5, pp. 2475–2482, 1997.

[5] N. Maggio, E. Shavit Stein, and M. Segal, "Ischemic LTP: NMDA-dependency and dorso/ventral distribution within the hippocampus," *Hippocampus*, vol. 25, no. 11, pp. 1465–1471, 2015.

[6] P. Quintana, S. Alberi, D. Hakkoum, and D. Muller, "Glutamate receptor changes associated with transient anoxia/hypoglycaemia in hippocampal slice cultures," *European Journal of Neuroscience*, vol. 23, no. 4, pp. 975–983, 2006.

[7] G. Deng, J. E. Orfila, R. M. Dietz et al., "Autonomous CaMKII activity as a drug target for histological and functional neuroprotection after resuscitation from cardiac arrest," *Cell Reports*, vol. 18, no. 5, pp. 1109–1117, 2017.

[8] N. Wang, L. Chen, N. Cheng, J. Zhang, T. Tian, and W. Lu, "Active calcium/calmodulin-dependent protein kinase II (CaMKII) regulates NMDA receptor mediated post-ischemic long-term potentiation (i-LTP) by promoting the interaction between CaMKII and NMDA receptors in ischemia," *Neural Plasticity*, vol. 2014, Article ID 827161, 10 pages, 2014.

[9] I. Buard, S. J. Coultrap, R. K. Freund et al., "CaMKII "autonomy" is required for initiating but not for maintaining neuronal long-term information storage," *The Journal of Neuroscience*, vol. 30, no. 24, pp. 8214–8220, 2010.

[10] V. Derkach, A. Barria, and T. R. Soderling, "Ca^{2+}/calmodulin-kinase II enhances channel conductance of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 6, pp. 3269–3274, 1999.

[11] C. E. Herron, R. A. J. Lester, E. J. Coan, and G. L. Collingridge, "Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism," *Nature*, vol. 322, no. 6076, pp. 265–268, 1986.

[12] R. C. Malenka and R. A. Nicoll, "Long-term potentiation–a decade of progress?," *Science*, vol. 285, no. 5435, pp. 1870–1874, 1999.

[13] M. Horn and W. Schlote, "Delayed neuronal death and delayed neuronal recovery in the human brain following global ischemia," *Acta Neuropathologica*, vol. 85, no. 1, pp. 79–87, 1992.

[14] T. Ng, D. I. Graham, J. H. Adams, and I. Ford, "Changes in the hippocampus and the cerebellum resulting from hypoxic insults: frequency and distribution," *Acta Neuropathologica*, vol. 78, no. 4, pp. 438–443, 1989.

[15] X. Dai, L. Chen, and M. Sokabe, "Neurosteroid estradiol rescues ischemia-induced deficit in the long-term potentiation of rat hippocampal CA1 neurons," *Neuropharmacology*, vol. 52, no. 4, pp. 1124–1138, 2007.

[16] F. Gillardon, I. Kiprianova, J. Sandkuhler, K. A. Hossmann, and M. Spranger, "Inhibition of caspases prevents cell death of hippocampal CA1 neurons, but not impairment of hippocampal long-term potentiation following global ischemia," *Neuroscience*, vol. 93, no. 4, pp. 1219–1222, 1999.

[17] I. Kiprianova, J. Sandkühler, S. Schwab, S. Hoyer, and M. Spranger, "Brain-derived neurotrophic factor improves long-term potentiation and cognitive functions after transient forebrain ischemia in the rat," *Experimental Neurology*, vol. 159, no. 2, pp. 511–519, 1999.

[18] K. Mori, M. Yoshioka, N. Suda et al., "An incomplete cerebral ischemia produced a delayed dysfunction in the rat hippocampal system," *Brain Research*, vol. 795, no. 1-2, pp. 221–226, 1998.

[19] J. E. Orfila, K. Shimizu, A. K. Garske et al., "Increasing small conductance Ca^{2+}–activated potassium channel activity reverses ischemia-induced impairment of long-term potentiation," *European Journal of Neuroscience*, vol. 40, no. 8, pp. 3179–3188, 2014.

[20] R. M. Dietz, G. Deng, J. E. Orfila, X. Hui, R. J. Traystman, and P. S. Herson, "Therapeutic hypothermia protects against ischemia-induced impairment of synaptic plasticity following juvenile cardiac arrest in sex-dependent manner," *Neuroscience*, vol. 325, pp. 132–141, 2016.

[21] M. P. Hutchens, R. J. Traystman, T. Fujiyoshi, S. Nakayama, and P. S. Herson, "Normothermic cardiac arrest and cardiopulmonary resuscitation: a mouse model of ischemia-reperfusion injury," *Journal of Visualized Experiments*, vol. 54, no. 54, article e3116, 2011.

[22] J. Kofler, K. Hattori, M. Sawada et al., "Histopathological and behavioral characterization of a novel model of cardiac arrest and cardiopulmonary resuscitation in mice," *Journal of Neuroscience Methods*, vol. 136, no. 1, pp. 33–44, 2004.

[23] N. Quillinan, G. Deng, K. Shimizu et al., "Long-term depression in Purkinje neurons is persistently impaired following cardiac arrest and cardiopulmonary resuscitation in mice," *Journal of Cerebral Blood Flow & Metabolism*, vol. 37, no. 8, pp. 3053–3064, 2016.

[24] G. Deng, J. C. Yonchek, N. Quillinan et al., "A novel mouse model of pediatric cardiac arrest and cardiopulmonary resuscitation reveals age-dependent neuronal sensitivities to ischemic injury," *Journal of Neuroscience Methods*, vol. 222, pp. 34–41, 2014.

[25] Z. I. Bashir and G. L. Collingridge, "An investigation of depotentiation of long-term potentiation in the CA1 region of the hippocampus," *Experimental Brain Research*, vol. 100, no. 3, pp. 437–443, 1994.

[26] X. Guli, T. Tokay, T. Kirschstein, and R. Kohling, "Status epilepticus enhances depotentiation after fully established LTP in an NMDAR-dependent but GluN2B-independent manner," *Neural Plasticity*, vol. 2016, Article ID 6592038, 10 pages, 2016.

[27] C. C. Huang, Y. C. Liang, and K. S. Hsu, "Characterization of the mechanism underlying the reversal of long term potentiation by low frequency stimulation at hippocampal CA1 synapses," *Journal of Biological Chemistry*, vol. 276, no. 51, pp. 48108–48117, 2001.

[28] Y. Qi, N. W. Hu, and M. J. Rowan, "Switching off LTP: mGlu and NMDA receptor–dependent novelty exploration–induced depotentiation in the rat hippocampus," *Cerebral Cortex*, vol. 23, no. 4, pp. 932–939, 2013.

[29] A. J. Baker, M. H. Zornow, M. R. Grafe et al., "Hypothermia prevents ischemia-induced increases in hippocampal glycine concentrations in rabbits," *Stroke*, vol. 22, no. 5, pp. 666–673, 1991.

[30] D. Jabaudon, M. Scanziani, B. H. Gahwiler, and U. Gerber, "Acute decrease in net glutamate uptake during energy deprivation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 10, pp. 5610–5615, 2000.

[31] D. J. Rossi, T. Oshima, and D. Attwell, "Glutamate release in severe brain ischaemia is mainly by reversed uptake," *Nature*, vol. 403, no. 6767, pp. 316–321, 2000.

[32] N. Shimada, R. Graf, G. Rosner, A. Wakayama, C. P. George, and W. D. Heiss, "Ischemic flow threshold for extracellular glutamate increase in cat cortex," *Journal of Cerebral Blood Flow & Metabolism*, vol. 9, no. 5, pp. 603–606, 1989.

[33] K. Takata, Y. Takeda, T. Sato, H. Nakatsuka, M. Yokoyama, and K. Morita, "Effects of hypothermia for a short period on histologic outcome and extracellular glutamate concentration during and after cardiac arrest in rats," *Critical Care Medicine*, vol. 33, no. 6, pp. 1340–1345, 2005.

[34] P. Calabresi, D. Centonze, A. Pisani, L. M. Cupini, and G. Bernardi, "Synaptic plasticity in the ischaemic brain," *The Lancet Neurology*, vol. 2, no. 10, pp. 622–629, 2003.

[35] M. Di Filippo, A. Tozzi, C. Costa et al., "Plasticity and repair in the post-ischemic brain," *Neuropharmacology*, vol. 55, no. 3, pp. 353–362, 2008.

[36] K. Kocsis, L. Knapp, L. Gellert et al., "Acetyl-L-carnitine normalizes the impaired long-term potentiation and spine density in a rat model of global ischemia," *Neuroscience*, vol. 269, pp. 265–272, 2014.

[37] D. Nagy, K. Kocsis, J. Fuzik et al., "Kainate postconditioning restores LTP in ischemic hippocampal CA1: onset-dependent second pathophysiological stress," *Neuropharmacology*, vol. 61, no. 5-6, pp. 1026–1032, 2011.

[38] G. N. Neigh, E. R. Glasper, J. Kofler et al., "Cardiac arrest with cardiopulmonary resuscitation reduces dendritic spine density in CA1 pyramidal cells and selectively alters acquisition of spatial memory," *European Journal of Neuroscience*, vol. 20, no. 7, pp. 1865–1872, 2004.

[39] Hypothermia after Cardiac Arrest Study Group, "Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest," *The New England Journal of Medicine*, vol. 346, no. 8, pp. 549–556, 2002.

[40] G. Lilja, N. Nielsen, H. Friberg et al., "Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C," *Circulation*, vol. 131, no. 15, pp. 1340–1349, 2015.

[41] M. Tiainen, E. Poutiainen, T. Kovala, O. Takkunen, O. Happola, and R. O. Roine, "Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia," *Stroke*, vol. 38, no. 8, pp. 2303–2308, 2007.

Hindawi
Neural Plasticity
Volume 2018, Article ID 3273246, 9 pages
https://doi.org/10.1155/2018/3273246

Research Article

Motor and Perceptual Recovery in Adult Patients with Mild Intellectual Disability

Mariagiovanna Cantone[1], **Maria A. Catalano**[2], **Giuseppe Lanza**[3], **Gaetano La Delfa**[2], **Raffaele Ferri**[3], **Manuela Pennisi**[4], **Rita Bella**[5], **Giovanni Pennisi**[6] and **Alessia Bramanti**[1]

[1]*IRCCS Centro Neurolesi Bonino Pulejo, Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy*
[2]*Associazione Assistenziale Villa Sandra, Via per Aci Bonaccorsi 16, San Giovanni La Punta, 95037 Catania, Italy*
[3]*Oasi Research Institute-IRCCS, Via Conte Ruggero 73, Troina, 94018 Enna, Italy*
[4]*Spinal Unit, Emergency Hospital "Cannizzaro", Via Messina 829, 95126 Catania, Italy*
[5]*Department of Medical and Surgical Sciences and Advanced Technologies, Section of Neurosciences, University of Catania, Via S. Sofia 78, 95123 Catania, Italy*
[6]*Department of Surgery and Medical-Surgical Specialties, University of Catania, Via S. Sofia 78, 95123 Catania, Italy*

Correspondence should be addressed to Giuseppe Lanza; glanza@oasi.en.it

Received 25 January 2018; Accepted 2 April 2018; Published 23 April 2018

Academic Editor: Steven W. Johnson

Introduction. The relationship between intellectual disability (ID) and hand motor coordination and speed-accuracy, as well as the effect of aging on fine motor performance in patients with ID, has been previously investigated. However, only a few data are available on the impact of the nonpharmacological interventions in adult patients with long-term hand motor deficit. *Methods*. Fifty adults with mild ID were enrolled. A group of thirty patients underwent a two-month intensive ergotherapic treatment that included hand motor rehabilitation and visual-perceptual treatment (group A); twenty patients performing conventional motor rehabilitation alone (group B) served as a control group. Data on attention, perceptual abilities, hand dexterity, and functional independence were collected by a blind operator, both at entry and at the end of the study. *Results*. After the interventions, group A showed significantly better performance than group B in all measures related to hand movement from both sides and to independence in activities of daily living. *Discussion*. Multimodal integrated interventions targeting visual-perceptual abilities and motor skills are an effective neurorehabilitative approach in adult patients with mild ID. Motor learning and memory-mediated mechanisms of neural plasticity might underlie the observed recovery, suggesting the presence of plastic adaptive changes even in the adult brain with ID.

1. Introduction

Intellectual disability (ID) is the most common development disorder, affecting approximately 1% of the general population in Europe [1]. ID typically impairs psychomotor skills and limits the abilities of daily living. A number of factors are associated with ID, including genetic and congenital causes (such as Down's syndrome (DS)), toxin exposure, infections, prematurity, birth injuries, and perinatal hypoxia, although most cases are of unknown etiology. Life expectancy has recently risen, but it still remains lower than that of the general population [2]. Moreover, epilepsy, behavioral disorders, and other medical diseases are frequent comorbidities and cause need for polypharmacotherapy and long-term social and health care [3]. Finally, adults with ID (namely, those with DS [4]) show a higher risk to develop dementia [5], which is characterized by a frequent and early tendency to lose independence and be institutionalized.

Subjects with ID are commonly described as being "clumsy" and with poor motor coordination, difficulty in both

fine and gross movements and motor planning. The combination of cognitive and long-standing sensory-motor deficits generally causes a variable degree of upper limb disability, which impairs even common activities of daily living, such as grasping small objects or the hand-finger movements. In addition, these patients tend to have a greater prevalence of physical decline compared to the aged general population, especially in terms of motor speed and accuracy of purposeful movements [6]. Recently, the relationship between ID and motor impairment concerning the areas of coordination, hand dexterity, and movement speed has attracted increasing attention [7–10]. In particular, the analysis of measures of reaction time and finger dexterity indicates that people with DS have more difficulty in performing fine movements [11]. On the other hand, it is known that normal aging interferes with fine motor performances [12, 13], and, therefore, the age-related decline of motor performance might be more pronounced in people with ID for tasks that are under perceptual or motor constraints, such as movement accuracy, speed, and reaction time. This is in line with the evidence that ID subjects usually display limitations in functional use of the hands, ranging from a mild deficit of in-hand manipulation to a severe impairment that makes grasping or holding an object even impossible [14].

As known, movement control and motor learning are driven by multiple sensory inputs. For instance, when the arm control is impaired, vision and other sensorial modalities, such as proprioception, can all support the arm movements and guide the necessary adjustments for correcting the errors. In this context, the spatial perception has a pivotal role in the development of motor skills and in particular in the Euclidean representation of the environment. This refers to a subtype of intuitive or natural geometry, which is largely a cross-cultural universal ability resulting from inherent properties of the human mind [15, 16]. More in detail, motor achievements may be integrated in the domains of tactile perception and depth perception. Usually, there is a high degree of concordance between the developmental stage in which certain perceptual sensitivities unfold and the corresponding onset of motor abilities [17, 18]. In patients with ID, both motor and perceptual developments are known to be impaired [19]. More recently, an altered perception of Euclidean geometry has been described in a group of children with symptoms of nonverbal disability, highlighting the relevance of the Euclidean perception also in cognitive tasks [20]. In this view, the rehabilitative-induced enhancement of the spatial perception might improve the efficacy of hand motor coordination during the object manipulation [21]. Similar approaches were previously and successfully applied also in patients recovering from mild-to-severe brain injury, as well as in a large cohort of children with mild ID [21, 22].

Based on this theoretical background, the aim of the present study was to assess and compare clinical data of motor dexterity in a group of adult patients with mild ID before and after ergotherapic activities involving Euclidean perception. This is to evaluate the efficacy on fine movement recovery and to indirectly probe any plastic change occurring in the adult brain with ID.

2. Materials and Methods

2.1. Participants. A group of 50 adult patients attending the Rehabilitation Department of the "Associazione Assistenziale Villa Sandra" in San Giovanni La Punta (Italy) were enrolled. All subjects met the diagnostic criteria of ID according to the American Association on Intellectual and Developmental Disabilities [23] and the Diagnostic and Statistical Manual of Mental Disorders-IV Edition (DSM-IV) [24]. They also showed significant impairment of global mental abilities, significant deficit of one or more areas of adaptive behaviour across multiple environments, and evidence that these limitations became apparent in their childhood or adolescence. Patients with mild ID (IQ = 50–69), rated by the intelligence quotient (IQ) scores defined by the Wechsler Abbreviated Scale of Intelligence [25] were included. Moreover, after a careful clinical evaluation, patients with IQ 70–79 (the so-called "borderline status") were also included due to their severe impairment in adaptive functioning.

Patients were divided into two groups: group A (30 patients, 15 females; median age 36.8 years, range 22–53 years; median IQ = 56.5, range 50–76), undergoing an intensive ergotherapic treatment that included both motor hand rehabilitation and cognitive-perceptual treatment, and group B (20 patients, 10 females; median age 38.7 years, range 27–45; median IQ = 55.0, range 50–70), performing conventional motor rehabilitation alone. All patients continued to receive their medical treatment, as well as usual health and recreational activities. Demographic and clinical characteristics of both groups at baseline are summarized in Table 1.

The condition underlying ID was unknown or not reported from one-third to one-half of the cases, whereas the remaining subjects were affected by DS. Patients with a severe ID, those who were unable to understand simple verbal orders, and subjects with a history of major psychiatric disorders or other neurological diseases (including dementia), those with acute or chronic not compensated medical illnesses, endocrinopathies, alcohol or drug abuse, and auditory or visual deficits, were excluded.

The study was approved by the local Ethics Committee and performed in accordance with the ethical standards of the Declaration of Helsinki in 1964 and its later amendments. Patients were enrolled after signing the informed consent.

2.2. Clinical Assessment. Clinical features were collected both at the entry of the study and after a period of two months of the interventions. The evaluation of patients with ID was a complex multifaceted process performed by both trained therapist and skilled physician. It encompassed an initial interview, followed by an informal assessment/clinical observation lasting from three to four hours, a neurological exam, and a formal assessment of cognitive, perceptual, and motor abilities using standardized scales, as described below. For some clinical variables, such as attention or praxis, a qualitative score was assigned from 0 to 3 on the basis of pure clinical observation (0 = normal; 1 = mild impairment; 2 = moderate impairment; and 3 = severe impairment). Similarly, the Euclidean perception of the space was scored from 0 to 2 (0 = normal perception; 1 = partial perception; and 2 = no perception).

Table 1: Demographic and clinical characteristics of patients at baseline.

	Group A	Group B
Number and gender	15 F/15 M	10 F/10 M
Median age, years	36.8 (range 22–53)	38.7 (range 27–45)
Median IQ, score	56.5 (range 50–76)	55.0 (range 50–70)
Handedness (R/L)	22/8	15/5

Group A: experimental group; Group B: control group; IQ: intelligence quotient; M: male; F: female; R: right-handed; L: left-handed.

Gross motor function was classified using the Italian version of the Gross Motor Function Classification System (GMFCS), expanded and revised [26]. GMFCS was originally developed for evaluating the severity of gross motor dysfunction of spontaneous movements, trunk control, and walking ability in children with cerebral palsy and other ID-associated disorders [27]. GMFCS is a 5-level classification system with an increasing gradient of gravity that differentiates patients with cerebral palsy based on their age current gross motor abilities and need for assistive technology and wheeled mobility. Patients classified in the level I can generally walk without restrictions, although tend to be limited in some of the more advanced motor skills; those classified at the level V are generally very limited in their ability to move themselves around, even with the use of assistive technology. This grading system has shown to be reliable across observers and with increasing age [28].

Bimanual Fine Motor Function (BFMF) is a classification of the hand function in children with cerebral palsy based on a five-level scale, whereby level I describes the best and level V the most limited function [29, 30]. BFMF can usefully describe and classify the fine motor capacity, providing additional information when used together with the Manual Ability Classification System (MACS) [31]. The latter is a classification of how patients with cerebral palsy use their hands when handling objects in daily activities with a focus on the use of both hands together, and it is extensively used in both clinical practice and research setting, providing relevant and reliable information on manual performance [31, 32]. As mentioned above, MACS also includes 5 levels of severity, the level I being the least affected (difficulty only in tasks needing speed and accuracy), and the level V the most impaired (not able to handle objects and severely limited abilities even for simple actions).

Data on hand motor dexterity were collected by using the Nine Hole Peg Test (NHPT), which is a widely validated measure used in several disorders [33, 34]. NHPT requires participant to repeatedly place and then remove nine pegs into nine holes, one each time, as quickly as possible. Score is influenced by muscle strength, tactile sensitivity of the thumb, and presence of intention tremor. The time needed to complete the task in seconds is the most frequently reported metric in the literature. In addition to the motor functioning, NHPT probes also the hand-eye coordination in patients with ID [35].

All evaluations were performed in a dedicated and quiet room, with a standardized set of verbal instructions followed by a demonstration of the task. Hand dominance was determined by the Edinburgh Handedness Inventory [36], and the dominant hand was the first to be tested. Functional status was assessed by the Activity Daily Living (ADL) and the Instrumental Activity Daily Living (IADL) scales.

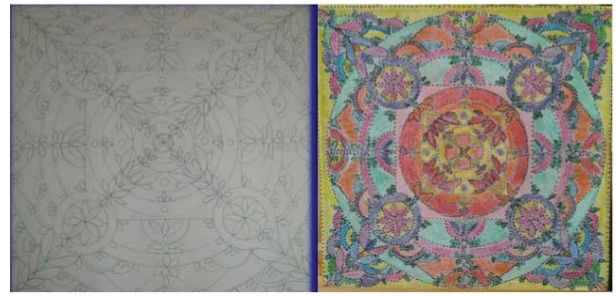


Figure 1: Example of a mandala figure (left side: template; right side: completed figure).

2.3. Ergotherapic Activities. Group A underwent occupational therapy targeting the rehabilitation of Euclidean spatial perception and hand motor functions through a graphic-motor protocol using a geometric pattern resembling the mandala figures (Figure 1) [17]. The basic form of most of the graphics was a square with four gates containing a circle with a center point. The use of this protocol was based both on the ecological approach of perceptual learning as a process of seeing the differences in the perceptual field around an individual and on the Piaget's theory of perceptual development [17, 18]. Every picture used in this study was designed considering the following parameters: ability to recognize an open space from a closed one; curved visual capability; simple or complex structured visual skills in relation to the figure; Euclidean perception; and ability to monitor the visual representation of the graphic segment. Specifically, during the activities, the following skills were established: ability to recognize a center point and the main parts of the picture; capacity to discriminate different configurations; ocular-manual coordination; ability to adequately place topological parameters; and ability to differentiate chromatic tracks.

Each patient, supervised by a skilled operator, started by composing the figure from simple sequences of lines intersecting in the canvas by obtaining a center. From this focal point, the participant builds simple and flat geometric shapes without the Euclidean representation (first level of ergotherapic protocol). Then, by using colours, the size, distance, shape, and orientation of the surfaces were highlighted (second level). By using a further geometric stratification, the depth of the picture was obtained (third level). In the fourth and last level of the ergotherapic protocol, subjects decorated every single part of the picture on a chromatic basis, providing circular or sinusoid lines. The graphical tools, such as pencils, paint brushes, and watercolours, were chosen based on the graphical ability and the residual capacity to control the imprinted force in the hand and its maintenance during each chronological step.

Conventional motor rehabilitation protocol included a daily session, ranging from 45 to 60 minutes, of progressive resistance/strength-based exercises of the upper limbs. The interventions were delivered by a trained physiotherapist.

Table 2: Assessment of the two groups of patients at baseline.

(a)

Clinical evaluation	Group A		Group B	
	Normal	Mild-moderate-severe impairment	Normal	Mild-moderate-severe impairment
Attention	1	8-21-0	1	7-12-0
Visual system	14	16-0-0	16	4-0-0
Auditory system	26	4-0-0	20	0-0-0
Sensory system	29	1-0-0	20	0-0-0
Motor system	21	9-0-0	12	8-0-0
Euclidean perception	0	16-14-0	0	20-0-0
Strength of the hand	4	13-11-2	16	4-0-0
Grasping	8	17-4-1	15	5-0-0
Linear palmar movement	8	18-4-0	16	4-0-0
Circular palmar movement	4	20-6-0	7	11-2-0
Handling	12	15-3-0	17	3-0-0
Finger holding	14	13-3-0	19	1-0-0

(b)

Formal evaluation	Group A			Group B				
	Median	Lower Q	Upper Q	Median	Lower Q	Upper Q	M-W "U"	p
NHPT3 left	18.2	15.9	21.3	18.8	17.3	20.1	247.0	NS
NHPT2 left	18.8	16.9	22.6	20.5	18.6	22.0	240.0	NS
NHPT1 left	20.8	17.2	22.7	21.7	18.6	22.8	242.0	NS
NHPT3 right	18.3	14.9	22.0	19.6	16.3	22.9	264.5	NS
NHPT2 right	18.6	15.6	23.7	20.8	16.9	24.6	259.0	NS
NHPT1 right	19.7	15.5	28.0	21.2	17.9	25.1	266.0	NS
IADL	7.0	5.0	8.0	5.0	2.0	8.0	211.0	NS
ADL	5.0	4.0	6.0	4.5	3.0	6.0	247.5	NS
MACS	2.0	2.0	2.0	1.5	1.0	2.0	240.0	NS
BFMF	1.0	1.0	2.0	1.0	1.0	2.0	285.0	NS
GMFCS	1.0	1.0	2.0	1.0	1.0	2.0	267.0	NS

Group A: experimental group; Group B: control group; M: male; F: female; R: right-handed; L: left-handed; NHPT: Nine Hole Peg Test; IADL: instrumental activity of daily living; ADL: activity of daily living; MACS: Manual Ability Classification System; BFMF: Bimanual Fine Motor Function; GMFCS: gross motor function classification system; Q: quartile; M-W: Mann–Whitney test; NS: not significant.

2.4. Statistical Analysis. Because of the nonnormal distribution of data (assessed by means of the Shapiro-Wilk W test), the nonparametric Mann–Whitney test for independent data sets was used to compare data from the two groups. Differences in symptom frequency between baseline and after treatment were evaluated by means of the chi-square test or the Fisher exact test (when any expected frequency was below 5). A p level of 0.05 was considered statistically significant.

3. Results

At the entry, all patients exhibited impairment of attention, sensory-motor functioning, and Euclidean perception; conversely, they were able to perform gross motor skills (such as running), although balance and coordination were partially limited. Therefore, they were able to walk at home and in outdoor spaces and to climb stairs without the use of railings. As shown in Table 2, patients exhibited a level I according to GMFCS. When considering the fine motor function (i.e., the capacity to grasp, hold, and manipulate objects for each hand separately), they were classified within the level 1 according to BFMF and within the level 2 for group A and 1 for group B according to MACS.

All participants successfully concluded the rehabilitation protocol without the need of any special accommodation. Attention and Euclidean perception, together with different abilities of the hand (such as strength, grasping, palmar movements, handling, and finger holding), significantly improved in group A only ($p < 0.001$). A significant improvement of almost all formal measures of hand movements was observed in both groups, although with better results in patients under the experimental condition. In particular, we observed a better response for measures of bimanual dexterity in group A compared to group B (ΔBFMF: -1.0 versus 0.1, $p = 0.019$; ΔMACS: -1.9 versus -1.3, $p = 0.018$). Finally, a

Table 3: Scores at the end of the rehabilitation protocol in the group A (scores did not significantly change in the group B performing conventional motor rehabilitation alone).

T	Normal	Mild-moderate-severe impairment	Chi-square	p
Attention				
T0	1	8-21-0	22.5	**<0.0001**
T1	12	14-4-0		
Visual system				
T0	14	16-0-0	0	NS
T1	14	16-0-0		
Auditory system				
T0	26	4-0-0	*	NS
T1	26	4-0-0		
Sensory system				
T0	29	1-0-0	*	NS
T1	29	1-0-0		
Motor system				
T0	21	9-0-0	0	NS
T1	21	9-0-0		
Strength of the hand				
T0	4	13-11-2	5.97	**<0.05**
T1	12	11-7-0		
Grasping				
T0	8	17-4-1	*	**<0.014**
T1	18	11-1-0		
Linear palmar movement				
T0	8	18-4-0	*	**<0.043**
T1	18	10-2-0		
Circular palmar movement				
T0	4	20-6-0	*	**<0.0018**
T1	17	10-3-0		
Handling				
T0	12	15-3-0	*	**<0.0038**
T1	24	5-1-0		
Fingers holding				
T0	14	13-3-0	*	**<0.01**
T1	25	4-1-0		
Euclidean perception				
T0	0	16-14-0	15.77	**0.0004**
T1	12	12-6-0		

T: timing; T0: baseline; T1: after experimental treatment; NS: not significant; numbers in bold: statistically significant p values; *: Fisher exact test.

significant amelioration of both IADL and ADL was obtained in group A only (ΔIADL: −1.2 versus 0.4, $p = 0.037$; ΔADL: −1.0 versus 1.0, $p = 0.008$). Data on motor and sensory abilities at the end of the ergotherapic training are shown in Tables 3 and 4.

4. Discussion

The main finding of this study shows a significant improvement of attention and Euclidean perception together with different motor abilities of the hand in adult patients with mild ID undergoing a two-month training of ergotherapic treatment focusing on visual-perceptual and hand motor functions. In the experimental group, we also observed a better response for measures of bimanual dexterity and independence in activities of daily living. As previously reported [37], adults with ID score poorly in manual tasks that recruit motor and visual abilities, being this considered as a consequence of the ID per se and an acquired motor or visual impairment secondary to the brain aging. In this context, the observed results underline that a multimodal integrated rehabilitative approach based on both physical and visual-perceptual training in a dedicated center might be more effective than the conventional therapy alone.

Table 4: Changes of motor hand functions and independence scores at the end of the protocol.

	Group A			Group B				
	Median	Lower Q	Upper Q	Median	Lower Q	Upper Q	M-W "*U*"	*p*
NHPT3 left	0.0	0.0	0.0	0.0	0.0	0.0	300.0	NS
NHPT2 left	0.0	0.0	0.0	0.0	0.0	0.0	300.0	NS
NHPT1 left	−1.0	−1.0	0.0	0.0	0.0	0.0	110.0	**0.0002**
NHPT3 right	0.0	0.0	0.0	0.0	0.0	0.0	270.0	NS
NHPT2 right	0.0	0.0	0.0	0.0	0.0	0.0	300.0	NS
NHPT1 right	−1.9	−4.2	0.7	0.0	−1.3	2.0	180.5	**0.018**
IADL	−1.2	−3.3	0.7	0.4	0.0	0.7	194.0	**0.037**
ADL	−1.0	−2.4	0.5	1.0	−0.7	1.5	165.0	**0.008**
MACS	−1.9	−3.8	0.0	0.2	−1.3	1.1	166.5	**0.018**
BFMF	−1.0	−2.5	0.6	0.1	0.0	0.5	167.0	**0.019**
GMFCS	0.0	−2.3	2.0	0.0	−0.8	0.8	260.0	NS

Group A: experimental group; Group B: control group; NHPT: Nine Hole Peg Test; IADL: instrumental activity of daily living; ADL: activity of daily living; MACS: Manual Ability Classification System; BFMF: Bimanual Fine Motor Function; GMFCS: gross motor function classification system; Q: quartile; M-W: Mann–Whitney test; NS: not significant; numbers in bold: statistically significant *p* values.

In the present study, the recovery of some motor performances meant as a reappropriation of each single component of a complex movement and perceptual ability. Indeed, to complete the Euclidean task, patients were required to optimize their gross and fine motor praxis, to have a proper exploration of the space, and to correctly quantify the force to be impressed on their hand. In addition, this type of intervention significantly motivated participants and tended to keep constant their attentive focus, suggesting that the "hand-eye-mind" pathway may act as a compensatory mechanism for the ID-associated deficits. Notably, all these steps are preparatory and necessary to possibly gain further recovery of increasingly complex abilities. Hand-eye coordination is a complex cognitive ability as it calls for a strong relationship between visual and manual motor systems. This integrated relationship finely coordinates motor responses of both eye and hand to produce controlled, rapid, and accurate movements. This system is of crucial importance for the normal child development, but it is also relevant for activities of daily living in adult people. Indeed, deficit of ocular or manual control has been studied also after an acquired brain injury [38].

From a neuroanatomical perspective, motor learning requires the development and retention of several skills, depending on the structural and functional integrity of the neostriatum and the cerebellum. These areas are also supported by a large cerebral network modulating both ocular and manual motor control. Indeed, the anatomophysiology of the human eye movement control is due to a wide interconnected system of cortical and subcortical structures that includes the frontal and parietal eye fields, the prefrontal cortex, the supplementary eye field, the basal ganglia, and the cingulate eye field [39]. Motor and premotor cortices, together with the somatosensory cortex, the cerebellum, and the basal ganglia, are all engaged in reaching an optimal motor control [40–42].

Interestingly, the study provides evidence that specific processes of motor learning and memory-mediated plastic mechanisms of recovery might occur also in the adult brain with ID, supporting the role of rehabilitation even for adult people with chronic pathologies. Nevertheless, the approach and setting for this type of patients are rather challenging, often requiring comprehensive services by different rehabilitation professionals to ensure that multidimensional issues can be successfully addressed. Accordingly, patients with ID should be guided by a complex ergotherapic process, through which they can reacquire, totally or partially, the spectrum of cognitive, perceptual, and motor skills that are impaired, from the basic skills to the more complex ones, in the same sequence they were first acquired during the normal development. The goal is to restore the disrupted brain processes underlying motor cognitive operations, in order to promote an accurate and efficient functioning which is based on proper sensory integration and powerful information processing. Finally, an active participation in meaningful and purposeful ergotherapic activities promotes motivation and improves subject's feelings, attitudes, and behaviors.

As known, plastic cortical changes are considered to be the substrate of learning and memory, both in development and aging and in physiological and pathological conditions. Several mechanisms are involved in the induction and modulation of neural plasticity, including phenomena of long-term potentiation and long-term depression, second messenger pathway activation, gene transcription, and morphological changes in neuronal membranes, axons, and postsynaptic cells [42]. Previous studies showed that the impairment of learning and memory in ID might result from a deficient synaptic plasticity due to several pathological processes, such as aberrant protein expression, altered molecular rearrangement, and excitatory-inhibitory neurotransmitter imbalance, eventually leading to maladaptive changes in neuronal circuitry [43–46]. Recently, noninvasive brain stimulation techniques have been used to assess the *in vivo* functional integrity of intracortical neurons and corticalspinal fibers [47, 48], to probe and monitor the excitability and connectivity of the human brain [49–53], and to modulate neural plasticity or even revert maladaptive plasticity [54–58], thus providing intriguing insights into the

pathophysiology and neurochemistry of several neurological and psychiatric disorders [59–65]. These techniques have been successfully applied also in patients with DS, fragile X syndrome, and low-functioning autism [66–68], as well as to promote motor recovery in patients with chronic stroke [69–71]. Overall, these findings open new exciting windows into the noninvasive rehabilitative interventions targeting cortical plasticity and neural connectivity. Finally, relatively little is known on the aberrant plasticity and/or metaplasticity in adults with ID [72, 73]. In this frame, further neurophysiological studies are encouraged to design experimental protocols based on physical activity, cognitive training, and innovative drugs.

The main limitations of this study are the relatively small number of participants and the lack of a follow-up study to prove the long-term effects of the intervention. In addition, although group A was very homogeneous in terms of clinical demographic features and age-matched with controls, it had more patients with moderate ID compared to the other groups; therefore, we cannot exclude that this might have partially influenced the results.

5. Conclusions

A combined intervention targeting motor and visual-perceptual skills is clinically and functionally effective in adults with mild ID, suggesting that neuroplastic adaptive changes may take place even in the adulthood of these patients. The underlying mechanisms will be further defined possibly combining different electrophysiological and neuroimaging techniques (such as high-density electroencephalography, transcranial magnetic stimulation, magnetoencephalography, and functional magnetic resonance imaging). Future studies are needed to clarify the impact of rehabilitative interventions on neural plasticity of motor and nonmotor cortical areas, to identify those subjects who would most likely respond to a specific intervention modality, to set up customized protocols, and to establish proper timing of observation and measures of outcome.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

[1] H. U. Wittchen, F. Jacobi, J. Rehm et al., "The size and burden of mental disorders and other disorders of the brain in Europe 2010," *European Neuropsychopharmacology*, vol. 21, no. 9, pp. 655–679, 2011.

[2] F. Tyrer, L. K. Smith, and C. W. McGrother, "Mortality in adults with moderate to profound intellectual disability: a population-based study," *Journal of Intellectual Disability Research*, vol. 51, no. 7, pp. 520–527, 2007.

[3] M. Haveman, J. Perry, L. Salvador-Carulla et al., "Ageing and health status in adults with intellectual disabilities: results of the European POMONA II study," *Journal of Intellectual & Developmental Disability*, vol. 36, no. 1, pp. 49–60, 2011.

[4] M. McCarron, P. McCallion, E. Reilly, and N. Mulryan, "A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome," *Journal of Intellectual Disability Research*, vol. 58, no. 1, pp. 61–70, 2014.

[5] M. P. Janicki and A. J. Dalton, "Prevalence of dementia and impact on intellectual disability services," *Mental Retardation*, vol. 38, no. 3, pp. 276–288, 2000.

[6] T. I. M. Hilgenkamp, D. Reis, R. van Wijck, and H. M. Evenhuis, "Physical activity levels in older adults with intellectual disabilities are extremely low," *Research in Developmental Disabilities*, vol. 33, no. 2, pp. 477–483, 2012.

[7] S. Kelly and E. G. Jessop, "A comparison of measures of disability and health status in people with physical disabilities undergoing vocational rehabilitation," *Journal of Public Health Medicine*, vol. 18, no. 2, pp. 169–174, 1996.

[8] N. Inui, M. Yamanishi, and S. Tada, "Simple reaction times and timing of serial reactions of adolescents with mental retardation, autism, and Down syndrome," *Perceptual and Motor Skills*, vol. 81, no. 3, pp. 739–745, 1995.

[9] M. L. Latash, N. Kang, and D. Patterson, "Finger coordination in persons with Down syndrome: atypical patterns of coordination and the effects of practice," *Experimental Brain Research*, vol. 146, no. 3, pp. 345–355, 2002.

[10] E. Carmeli, S. Kessel, S. Bar-Chad, and J. Merrick, "A comparison between older persons with down syndrome and a control group: clinical characteristics, functional status and sensorimotor function," *Down's Syndrome, Research and Practice*, vol. 9, no. 1, pp. 17–24, 2004.

[11] E. Kioumourtzoglou, S. Batsiou, Y. Theodorakis, and G. Mauromatis, "Selected motor skills of mentally retarded and nonretarded individuals," *Perceptual and Motor Skills*, vol. 78, no. 3, pp. 1011–1015, 1994.

[12] S. A. Fraser, K. Z. H. Li, and V. B. Penhune, "Dual-task performance reveals increased involvement of executive control in fine motor sequencing in healthy aging," *The Journals of Gerontology: Series B*, vol. 65B, no. 5, pp. 526–535, 2010.

[13] E. J. Corti, A. R. Johnson, H. Riddle, N. Gasson, R. Kane, and A. M. Loftus, "The relationship between executive function and fine motor control in young and older adults," *Human Movement Science*, vol. 51, pp. 41–50, 2017.

[14] M. Arner, A. C. Eliasson, S. Nicklasson, K. Sommerstein, and G. Hägglund, "Hand function in cerebral palsy. Report of 367 children in a population-based longitudinal health care program," *The Journal of Hand Surgery*, vol. 33, no. 8, pp. 1337–1347, 2008.

[15] E. Spelke, S. A. Lee, and V. Izard, "Beyond core knowledge: natural geometry," *Cognitive Science*, vol. 34, no. 5, pp. 863–884, 2010.

[16] J. P. Spencer, L. B. Smith, and E. Thelen, "Tests of a dynamic systems account of the A-not-B error: the influence of prior experience on the spatial memory abilities of two-year-olds," *Child Development*, vol. 72, no. 5, pp. 1327–1346, 2001.

[17] J. J. Gibson, *The Ecological Approach to Visual Perception: Classic Edition*, Psychology Press & Routledge Classic Editions, New York, NY, 1st edition, 2014.

[18] B. Inhelder, J. Piaget, A. Parsons, and S. Milgram, *The Growth of Logical Thinking from Childhood to Adolescence*, Basic Books, New York, NY, USA, 1958.

[19] F. D. D. Blasi, F. Elia, S. Buono, G. J. A. Ramakers, and S. F. D. Nuovo, "Relationships between visual-motor and cognitive

abilities in intellectual disabilities," *Perceptual and Motor Skills*, vol. 104, no. 3, pp. 763–772, 2007.

[20] I. C. Mammarella, C. Meneghetti, F. Pazzaglia, and C. Cornoldi, "Memory and comprehension deficits in spatial descriptions of children with non-verbal and reading disabilities," *Frontiers in Psychology*, vol. 5, 2015.

[21] Y. P. Wuang, C. C. Wang, M. H. Huang, and C. Y. Su, "Prospective study of the effect of sensory integration, neurodevelopmental treatment, and perceptual-motor therapy on the sensorimotor performance in children with mild mental retardation," *American Journal of Occupational Therapy*, vol. 63, no. 4, pp. 441–452, 2009.

[22] T. Westfall, K. Moore, M. Kulkarni, E. Cook, and M. de Leon, "Cognitive perceptual motor retraining: remediation of deficits following brain injury," *Journal of Cognitive Rehabilitation, Winter*, pp. 5–11, 2005.

[23] R. L. Schalock, S. A. Borthwick-Duffy, V. J. Bradley et al., *Intellectual Disability: Definition, Classification, and Systems of Supports*, American Association on Intellectual and Developmental Disabilities, 444 North Capitol Street NW Suite 846, Washington, DC, 20001, USA, 2010.

[24] American Psychiatric Association, *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Press Inc, Washington DC, USA, 4th edition, 1994.

[25] J. R. Hays, D. L. Reas, and J. B. Shaw, "Concurrent validity of the Wechsler abbreviated scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients," *Psychological Reports*, vol. 90, no. 2, pp. 355–359, 2002.

[26] R. J. Palisano, P. Rosenbaum, D. Bartlett, and M. H. Livingston, "Content validity of the expanded and revised gross motor function classification system," *Developmental Medicine & Child Neurology*, vol. 50, no. 10, pp. 744–750, 2008.

[27] N. Chrysagis, E. K. Skordilis, and D. Koutsouki, "Validity and clinical utility of functional assessments in children with cerebral palsy," *Archives of Physical Medicine and Rehabilitation*, vol. 95, no. 2, pp. 369–374, 2014.

[28] C. Morris and D. Bartlett, "Gross motor function classification system: impact and utility," *Developmental Medicine & Child Neurology*, vol. 46, no. 1, pp. 60–65, 2004.

[29] E. Beckung and G. Hagberg, "Neuroimpairments, activity limitations, and participation restrictions in children with cerebral palsy," *Developmental Medicine & Child Neurology*, vol. 44, no. 5, pp. 309–316, 2002.

[30] M. Nystrand, E. Beckung, H. Dickinson, and A. Colver, "Stability of motor function and associated impairments between childhood and adolescence in young people with cerebral palsy in Europe," *Developmental Medicine & Child Neurology*, vol. 56, no. 9, pp. 833–838, 2014.

[31] A. C. Eliasson, L. Krumlinde-Sundholm, B. Rösblad et al., "The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability," *Developmental Medicine & Child Neurology*, vol. 48, no. 7, pp. 549–554, 2006.

[32] D. Jeevanantham, E. Dyszuk, and D. Bartlett, "The manual ability classification system: a scoping review," *Pediatric Physical Therapy*, vol. 27, no. 3, pp. 236–241, 2015.

[33] B. C. Tobler-Ammann, E. D. de Bruin, M. C. Fluet, O. Lambercy, R. A. de Bie, and R. H. Knols, "Concurrent validity and test-retest reliability of the Virtual Peg Insertion Test to quantify upper limb function in patients with chronic stroke," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, no. 1, pp. 8–18, 2016.

[34] P. Feys, I. Lamers, G. Francis et al., "The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis," *Multiple Sclerosis Journal*, vol. 23, no. 5, pp. 711–720, 2017.

[35] K. Oxford Grice, K. A. Vogel, V. Le, A. Mitchell, S. Muniz, and M. A. Vollmer, "Adult norms for a commercially available Nine Hole Peg Test for finger dexterity," *The American Journal of Occupational Therapy*, vol. 57, no. 5, pp. 570–573, 2003.

[36] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, 1971.

[37] E. Carmeli, T. Bar-Yossef, C. Ariav, R. Levy, and D. G. Liebermann, "Perceptual-motor coordination in persons with mild intellectual disability," *Disability and Rehabilitation*, vol. 30, no. 5, pp. 323–329, 2008.

[38] J. R. Rizzo, M. Hosseini, E. A. Wong et al., "The intersection between ocular and manual motor control: eye–hand coordination in acquired brain injury," *Frontiers in Neurology*, vol. 8, p. 227, 2017.

[39] K. N. Thakkar, F. M. Z. van den Heiligenberg, R. S. Kahn, and S. F. W. Neggers, "Frontal-subcortical circuits involved in reactive control and monitoring of gaze," *Journal of Neuroscience*, vol. 34, no. 26, pp. 8918–8929, 2014.

[40] G. E. Alexander, M. R. DeLong, and P. L. Strick, "Parallel organization of functionally segregated circuits linking basal ganglia and cortex," *Annual Review of Neuroscience*, vol. 9, no. 1, pp. 357–381, 1986.

[41] S. M. Rao, D. L. Harrington, K. Y. Haaland, J. A. Bobholz, R. W. Cox, and J. R. Binder, "Distributed neural systems underlying the timing of movements," *Journal of Neuroscience*, vol. 17, no. 14, pp. 5528–5535, 1997.

[42] J. D. Sweatt, "Neural plasticity and behavior - sixty years of conceptual advances," *Journal of Neurochemistry*, vol. 139, Supplement 2, pp. 179–199, 2016.

[43] J. Zorrilla de San Martin, J. M. Delabar, A. Bacci, and M. C. Potier, "GABAergic over-inhibition, a promising hypothesis for cognitive deficits in Down syndrome," *Free Radical Biology & Medicine*, vol. 114, pp. 33–39, 2018.

[44] E. Moretto, L. Murru, G. Martano, J. Sassone, and M. Passafaro, "Glutamatergic synapses in neurodevelopmental disorders," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*In press.

[45] S. C. Borrie, H. Brems, E. Legius, and C. Bagni, "Cognitive dysfunctions in intellectual disabilities: the contributions of the Ras-MAPK and PI3K-AKT-mTOR pathways," *Annual Review of Genomics and Human Genetics*, vol. 18, no. 1, pp. 115–142, 2017.

[46] M. Aincy, H. Meziane, Y. Herault, and Y. Humeau, "Synaptic dysfunction in amygdala in intellectual disorder models," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*In press.

[47] S. Groppa, A. Oliviero, A. Eisen et al., "A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee," *Clinical Neurophysiology*, vol. 123, no. 5, pp. 858–882, 2012.

[48] P. M. Rossini, D. Burke, R. Chen et al., "Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an

I.F.C.N. Committee," *Clinical Neurophysiology*, vol. 126, no. 6, pp. 1071–1107, 2015.

[49] G. Lanza, R. Bella, S. Giuffrida et al., "Preserved transcallosal inhibition to transcranial magnetic stimulation in nondemented elderly patients with leukoaraiosis," *BioMed Research International*, vol. 2013, Article ID 351680, 5 pages, 2013.

[50] A. Karabanov, U. Ziemann, M. Hamada et al., "Consensus paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation," *Brain Stimulation*, vol. 8, no. 5, pp. 993–1006, 2015.

[51] M. Pennisi, G. Lanza, M. Cantone et al., "Correlation between motor cortex excitability changes and cognitive impairment in vascular depression: pathophysiological insights from a longitudinal TMS study," *Neural Plasticity*, vol. 2016, Article ID 8154969, 10 pages, 2016.

[52] A. Suppa, A. Quartarone, H. Siebner et al., "The associative brain at work: evidence from paired associative stimulation studies in humans," *Clinical Neurophysiology*, vol. 128, no. 11, pp. 2140–2164, 2017.

[53] M. Pennisi, G. Lanza, M. Cantone et al., "Cortical involvement in celiac disease before and after long-term gluten-free diet: a transcranial magnetic stimulation study," *PLoS One*, vol. 12, no. 5, article e0177560, 2017.

[54] A. Naro, D. Milardi, M. Russo et al., "Non-invasive brain stimulation, a tool to revert maladaptive plasticity in neuropathic pain," *Frontiers in Human Neuroscience*, vol. 10, no. 10, p. 376, 2016.

[55] A. Quartarone, V. Rizzo, C. Terranova et al., "Therapeutic use of non-invasive brain stimulation in dystonia," *Frontiers in Neuroscience*, vol. 11, no. 11, p. 423, 2017.

[56] A. Leo, A. Naro, F. Molonia et al., "Spasticity management: the current state of transcranial neuromodulation," *PM&R*, vol. 9, no. 10, pp. 1020–1029, 2017.

[57] T. Soundara Rajan, M. F. M. Ghilardi, H. Y. Wang et al., "Mechanism of action for rTMS: a working hypothesis based on animal studies," *Frontiers in Physiology*, vol. 8, no. 457, 2017.

[58] G. Lanza, M. Cantone, D. Aricò et al., "Clinical and electrophysiological impact of repetitive low-frequency transcranial magnetic stimulation on the sensory–motor network in patients with restless legs syndrome," *Therapeutic Advances in Neurological Disorders*, vol. 11, pp. 1–12, 2018.

[59] C. Concerto, G. Lanza, M. Cantone et al., "Different patterns of cortical excitability in major depression and vascular depression: a transcranial magnetic stimulation study," *BMC Psychiatry*, vol. 13, no. 1, 2013.

[60] M. Cantone, G. Di Pino, F. Capone et al., "The contribution of transcranial magnetic stimulation in the diagnosis and in the management of dementia," *Clinical Neurophysiology*, vol. 125, no. 8, pp. 1509–1532, 2014.

[61] G. Pennisi, R. Bella, and G. Lanza, "Motor cortex plasticity in subcortical ischemic vascular dementia: what can TMS say?," *Clinical Neurophysiology*, vol. 126, no. 5, pp. 851-852, 2015.

[62] R. Bella, M. Cantone, G. Lanza et al., "Cholinergic circuitry functioning in patients with vascular cognitive impairment – no dementia," *Brain Stimulation*, vol. 9, no. 2, pp. 225–233, 2016.

[63] M. Cantone, A. Bramanti, G. Lanza et al., "Cortical plasticity in depression," *ASN Neuro*, vol. 9, no. 3, Article ID 1759091417711512, 2017.

[64] G. Lanza, P. Bramanti, M. Cantone, M. Pennisi, G. Pennisi, and R. Bella, "Vascular cognitive impairment through the looking glass of transcranial magnetic stimulation," *Behavioural Neurology*, vol. 2017, Article ID 1421326, 16 pages, 2017.

[65] G. Lanza, C. G. Bachmann, I. Ghorayeb, Y. Wang, R. Ferri, and W. Paulus, "Central and peripheral nervous system excitability in restless legs syndrome," *Sleep Medicine*, vol. 31, pp. 49–60, 2017.

[66] F. Battaglia, A. Quartarone, V. Rizzo et al., "Early impairment of synaptic plasticity in patients with Down's syndrome," *Neurobiology of Aging*, vol. 29, no. 8, pp. 1272–1275, 2008.

[67] L. M. Oberman, J. C. Horvath, and A. Pascual-Leone, "TMS: using the theta-burst protocol to explore mechanism of plasticity in individuals with fragile X syndrome and autism," *Journal of Visualized Experiments*, vol. 28, no. 46, 2010.

[68] S. Panerai, D. Tasca, B. Lanuzza et al., "Effects of repetitive transcranial magnetic stimulation in performing eye-hand integration tasks: four preliminary studies with children showing low-functioning autism," *Autism*, vol. 18, no. 6, pp. 638–650, 2014.

[69] P. Talelli, A. Wallace, M. Dileone et al., "Theta burst stimulation in the rehabilitation of the upper limb: a semirandomized, placebo-controlled trial in chronic stroke patients," *Neurorehabilitation and Neural Repair*, vol. 26, no. 8, pp. 976–987, 2012.

[70] G. Di Pino, G. Pellegrino, G. Assenza et al., "Modulation of brain plasticity in stroke: a novel model for neurorehabilitation," *Nature Reviews Neurology*, vol. 10, no. 10, pp. 597–608, 2014.

[71] V. Di Lazzaro, F. Capone, G. Di Pino et al., "Combining robotic training and non-invasive brain stimulation in severe upper limb-impaired chronic stroke patients," *Frontiers in Neuroscience*, vol. 10, no. 88, 2016.

[72] C. Mastroeni, T. O. Bergmann, V. Rizzo et al., "Brain-derived neurotrophic factor - a major player in stimulation-induced homeostatic metaplasticity of human motor cortex?," *PLoS One*, vol. 8, no. 2, article e57957, 2013.

[73] W. Kułak, W. Sobaniec, J. S. Kuzia, and L. Boćkowski, "Neurophysiologic and neuroimaging studies of brain plasticity in children with spastic cerebral palsy," *Experimental Neurology*, vol. 198, no. 1, pp. 4–11, 2006.