

# 2016 yearbook of neurorestoratology

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**Abstract:** Neurorestoratology, a new interdisciplinary field, has gradually become a popular clinical discipline. Physicians and scientists in the neurorestoration field have discovered new pathogenesises of nervous system diseases and damage, explored new neurorestorative mechanisms, and obtained improving neurorestorative effects in clinical trials (or therapies). This paper summarizes the major progress achieved over the past year.

**Keywords:** yearbook, neurorestoratology, pathogenesis, neural repair and regeneration, central nervous system disease, neurorestorative mechanisms, neurorestorative strategies

## Introduction

Patience is bitter, but its fruit is sweet. Neurorestoratology has gradually become a popular clinical discipline since it was first established as a formal field in 2008.<sup>1-4</sup> The International Association of Neurorestoratology (IANR), the professional association for this emerging interdisciplinary field, was set up in 2007. Then, the definition of this discipline was clearly made in Beijing Declaration of IANR in 2009.<sup>5</sup> The Journal of Neurorestoratology (IANR's official journal) published its first paper in 2013.<sup>6</sup> The Beijing Declaration of IANR was further clarified at the annual IANR conference in Tehran in 2015, which announced that "functional recovery is possible after CNS injury and neurodegeneration."<sup>7</sup> This was the first time in world history that a professional medical association repudiated Cajal's thesis<sup>8</sup> about nervous system regeneration. The goal of neurorestoratology is to restore, promote, and maintain the integrity of impaired or lost neuronal functions and structures – a previously elusive goal.<sup>7</sup> But over the past decade, several research papers<sup>9-11</sup> and review books<sup>12,13</sup> have documented advances in neurorestoration, including therapeutic achievements and exploration of theories and mechanisms. Increasing numbers of researchers, physicians, and even some governments are recognizing the importance of neurorestoratology, with state-funded research efforts such as the US Brain Project, European Human Brain Project, and Chinese and Japanese Brain Project[s] (currently being developed). These efforts are contributing greatly to the following goals: 1) to further identify pathogenesises of nervous system as well as psychological diseases or damage, including dysfunction of perception, movement, autonomic nerve, cognition, memory, intelligence, sleep, etc.; 2) to explore new neurorestorative mechanisms and put forward new neurorestorative theories; and 3) to develop better neurorestorative effects in clinical settings. Significant progress has been made toward all three goals, which we summarize below in the "2016 Yearbook of Neurorestoratology."

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## New pathogeneses of nervous system and psychological disease or damage

During the past year, further findings have been reported based on the basic and classic pathogeneses of nervous diseases or damage. Glasser et al<sup>14</sup> reported that a multimodal parcellation of the human cerebral cortex with machine-learning classifier as a tool could correctly locate areas in individuals with atypical parcellations. This breakthrough achievement has the potential to develop neuroanatomical precision of the structural and functional organization in the human cerebral cortex, its variation across individuals, and during the processes of development, aging, and disease.<sup>14</sup> Setting a powerful and efficient map of human neuroanatomy and functional connectivity can indicate functional representations in the brain.<sup>15</sup> Through a multimodal approach combining structural information and task-independent (*resting state* functional magnetic resonance imaging) and task-dependent functional connectivity, disrupted cortico-cingulo circuits were found to promote autism spectrum disorder deficits in attention and social interaction.<sup>16</sup>

Kamat et al<sup>17</sup> found that tau hyperphosphorylation and synapse dysfunction might result from oxidative stress, which was mediated through *N*-methyl-*D*-aspartate receptor and their interaction with other molecules. Higher expression of the common C4 allele or excessive complement activity could reduce numbers of synapses in the brains, which might be one cause for schizophrenia.<sup>18</sup> Further inappropriately activated microglia in adult brains could engulf synaptic material in a CR3-dependent process when exposed to soluble A $\beta$  oligomers, which might be one cause for the induction of synapse loss in Alzheimer's disease (AD).<sup>19</sup> Major drivers of neurodegeneration may result from complement activation and microglia-mediated synaptic pruning during progranulin deficiency.<sup>20</sup>

Kumar et al<sup>21</sup> found that while  $\beta$ -amyloid might play a protective role in innate immunity against infection or inflammatory stimuli, it might also drive amyloidosis and play a damaging role in AD. Normally, UBQLN2 (proteasome shuttle factor) mediates autophagy-independent clearance of protein aggregates by the proteasome. When there are mutations in UBQLN2, it can lead to neurodegeneration with defects in chaperone binding and impairment of aggregate clearance.<sup>22</sup>

## New neurorestorative mechanisms and theories

Kandul<sup>23</sup> reported that selectively removing deleterious genome or mutant mtDNA could achieve the goal of treating

mitochondrial and aging diseases, such as AD. García Santos<sup>24</sup> reported that spinal cord injection of bone marrow mononuclear cells for patients with amyotrophic lateral sclerosis (ALS) showed a distant beneficial effect in the brain, in which cells have longer survival and less disability with metabolic improvement. Further exploration needs to be done to know its exact mechanism. Through inhibiting excessively expressed DNA methyltransferases, the function of bone marrow mesenchymal stromal cells (MSCs) derived from ALS patients can be restored.<sup>25</sup>

## New clinical evidence for neurorestorative strategies

### Cell therapy

Cell-based therapies have been shown to improve the functional abilities of patients and their quality of life, particularly for those suffering from spinal cord injury (SCI), stroke, ALS, multiple sclerosis, cerebral palsy, AD, Parkinson's disease, traumatic brain injury, and other types of CNS diseases and damage.<sup>26</sup> Below, we summarize the new clinical evidence generated in 2016 for cell therapy to treat neurological disease and damage.

Chronic stroke was treated using human neural stem cells through stereotactic ipsilateral putamen injection,<sup>27</sup> using bone marrow-derived mesenchymal stem cells through stereotactic injection into the margin of the stroke,<sup>28</sup> and using autologous M2 cells through intrathecal administration.<sup>29</sup> These methods restored partial neurological function.

More evidence of improving function for patients with complete chronic SCI has been reported using a variety of different cell-based therapies, including umbilical cord blood-derived mononuclear cell transplants for spinal cord and locomotor training,<sup>30</sup> the mononuclear-enriched bone marrow cell transplantation through intrathecal infusion,<sup>31</sup> bone marrow MSC transplantation through lumbar puncture into subarachnoid space,<sup>32</sup> a combination of neuronal cells differentiated from autologous adipose tissue-derived mesenchymal stem cells, and hematopoietic stem cells through intrathecal infusion,<sup>33</sup> and olfactory mucosa lamina propria transplants into the spinal cord.<sup>34</sup>

Promising results for patients with ALS have been reported by intraspinal injection of bone marrow-derived neural stem cells, in which patients experienced a temporary stabilization for the first few months postinjection and then gradually deteriorated.<sup>35</sup> Transplantation of inducing mesenchymal stem cells to secrete neurotrophic factors by intramuscular and intrathecal injections has shown at least

25% improvement at 6 months after treatment in the slope of progression for patients with ALS.<sup>36</sup>

Even patients diagnosed with an aggressive form of multiple sclerosis over a prolonged period have substantially recovered their neurological function following autologous hemopoietic stem cell transplantation.<sup>37</sup> Canesi et al<sup>38</sup> reported that bone marrow MSC administration for patients with progressive supranuclear palsy could clinically stabilize the condition for at least 6 months, a significant outcome given the invariably rapid deterioration of motor function.

Cox et al<sup>39</sup> reported that intravenously delivered autologous bone marrow mononuclear cell infusion for severe adult traumatic brain injury appears to play a role in CNS structural preservation. Vaquero et al<sup>40</sup> found that intrathecal administration of autologous MSCs in patients with diffuse axonal injury could improve neurological functions and show a diffuse and progressive increase in brain glucose metabolism.

Some case reports also showed benefits of cell therapy for patients with postpoliomyelitis syndrome<sup>41</sup> and primary torsion dystonia.<sup>42</sup>

## Neuromodulation and the brain–computer interface

Neuromodulation and the brain–computer interface provides one of most promising strategies in neurorestoratology.<sup>13</sup> Bouton et al<sup>43</sup> reported that intracortically recorded signals could be decoded to extract information related to motion (imagined movements), allow paralyzed humans to restore cortical control of functional movement, and control computer and robotic arms through a custom-built high-resolution neuromuscular electrical stimulation system. Vansteensel et al<sup>44</sup> reported that the locked-in patient with ALS could accurately and independently control a computer typing program for autonomous communication with implanted brain–computer interface. Flesher et al<sup>45</sup> reported that intracortical microstimulation of the human somatosensory cortex could evoke tactile sensations perceived as originating from locations on the hand for patients with long-term SCI who had lost feeling. Donati et al<sup>46</sup> reported that eight paraplegic patients recovered partial neurological functions by 12-month training with a brain–machine interface-based gait protocol.

## Neurorestorative surgery

Several kinds of neurorestorative surgeries have been able to help patients with central nervous damage restore their neurological functioning<sup>13</sup> since Carlsson and Sundin<sup>47</sup> reported their results of reconstruction of efferent pathways

to the urinary bladder in 1967. Tuite et al<sup>48</sup> reported from their clinical trial that the Xiao procedure for restoring bladder and bowel function did not result in voluntary voiding or continence in any patient, but patients undergoing spinal cord detethering plus the Xiao procedure were more likely to have greater improvements in total bladder capacity, bladder overactivity control, and overall quality of life than those who underwent detethering only. The explanation for this improvement may be related to sacral nerve root sectioning, instead of reinnervation. Yang<sup>49</sup> reported that revascularization in sickle cell disease patients with Moyamoya syndrome could prevent stroke recurrence. Comparing various reanimation techniques such as facial nerve interpositional graft, hypoglossal–facial nerve transfer, and direct end-to-side facial–hypoglossal anastomosis, Mohamed et al<sup>50</sup> concluded that the latter technique through epineural suture is the most effective method with excellent outcomes for facial reanimation. Kochhar et al<sup>51</sup> reported that facial nerve direct end-to-end coadaptation to the hypoglossal nerve was effective in restoring facial tone and symmetry after facial paralysis.

## Pharmaceutical

So far, there are many pharmaceutical interventions for neurorestoration, but most of them have failed their aims when tested in clinical trials.<sup>13</sup> Although delivering granulocyte-colony stimulating factor is a feasible treatment for chronic stroke, a research study found that this did not demonstrate functional recovery.<sup>52</sup> More promising lines of research have demonstrated that erythropoietin and granulocyte-colony stimulating factor combination therapy may improve the functional abilities of stroke patients;<sup>53</sup> dl-3-n-butylphthalide significantly increased the level of circulation and improved clinical outcome in patients with acute ischemic stroke.<sup>54</sup>

## Summary

Much exploration has been done and many valuable results have been achieved over the course of 2016 for understanding the pathogenesis of nervous system diseases and damage, exploring neurorestorative mechanisms, and seeking more effective therapeutic strategies in the field of neurorestoratology. We firmly believe that there will be a step-by-step progress in neurorestoratology in the future, especially therapeutic strategies for improving neurorestorative effects. While the existing literature on cell therapies for CNS diseases and damage have demonstrated that these procedures are relatively safe and produce effective results, we still need more multicenter, randomized, controlled, double-blind studies and trials with larger sample sizes in order to establish the

long-term risks and benefits for patients now and in the near future – learning from yesterday and working harder today in order to make a better tomorrow.

## Disclosure

The authors report no conflicts of interest in this work.

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