

Brain restoration as an emerging field in neurology and neuroscience

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Abstract. Restoration of brain function was long thought to be impossible. However, as the publications in the journal *Restorative Neurology and Neuroscience* (RNN) for more than 20 years attest, clinically useful improvement can be achieved after damage or diseases of the brain, the retina, and the peripheral nervous system. By reviewing both pre-clinical studies and clinical work, we explore what advancements can be made today and what to expect going forward. For example, in the last few years we have seen a clinical focus in the area of non-invasive brain stimulations and rehabilitation training trials. In basic animal research multi-modal approaches have been presented to restore brain function with a combination of different treatments. We think that this is an exciting time in the area of restoration of brain function with many new strategies aimed at helping recovering their impaired neurological functions.

Keywords: Brain plasticity, neural repair, restoration, nervous system

1. Introduction

Restoration of brain function was long thought to be impossible. But the journal *Restorative Neurology and Neuroscience* (RNN), for more than 20 years, has helped the scientific community to better understand brain repair and to find new methods that are clinically useful to improve neurological functions after damage or diseases of the brain, the retina, and the peripheral nervous system. We now review both pre-clinical studies and clinical work during the last few years to see what has been achieved. In the clinical domain particularly the area of non-invasive brain stimulations has been a hot topic as has been the field of behavioral training in rehabilitation. In basic animal research multi-modal approaches to restore brain function have been presented with a combination of different treatments. We think that this is an exciting time in the

area of restoration of brain function with many new strategies aimed at helping recovering their impaired neurological functions.

2. Clinical studies

2.1. Behavioral studies and training

RNN published a number of clinical studies aiming to elucidate mechanisms of functional impairments in a range of conditions. This includes impairment of spatial memory deficits in attentional neglect (Luukainen-Markkula et al., 2011), or supposedly compensatory changes in allocation of spatial attention in deaf signers, with a focus on the bottom half of the face of the perceived person (Mitchell et al., 2013). Concerning visual system, alterations in fixational eye movements in amblyopia subjects was investigated by Shi et al. (2012) while Bergsma et al. (2011) used a driving simulator to test how oculomotor behaviour of hemianopia patients is changing after vision training. As somatosensory-motor system

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is considered a “model” to study neural plasticity, several groups expanded our knowledge within this field using behavioral, but also physiological methods, e.g. motor evoked potentials (Floeter et al., 2013; Vallence et al., 2012; Cimmino et al., 2013; Romano et al., 2013; Biamco et al., 2012). Concerning neurodegenerative conditions, it has been shown that in multiple-sclerosis the risk of cognitive decline can be reduced by education (Scarpazza et al., 2013). Finally, Yang & Bao (2013) reviewed recent studies of tinnitus providing evidence for downregulation of inhibition as a key mechanism behind hearing loss.

Further, efficacy of various treatment types was evaluated, including temporal information processing training to improve cognitive performance in elderly (Szelag & Skolimowska, 2012; Szelag et al., 2011). Tass et al. (2012) used a technique known as “acoustic coordinated reset” to de-synchronize neural activity in patients suffering from tinnitus, a study which was followed by a vivid discussion (Rücker & Antes, 2013; Tass et al., 2013). Caloric vestibular stimulation alleviated neglect in a case study of a patient with left-hemisphere lesion (Ronchi et al., 2013). Two studies investigated training protocols in stroke patients, e.g. using a foot stimulator (Ernst et al., 2013), or more complex protocols including different activities (De Diego et al., 2013). The modified constraint-induced therapy was reviewed by Page et al. (2013). Manella and Field-Fote (2013) studied the effects of locomotor training on spasticity in individuals with spinal cord injury. De Silva Camairão (2011) used virtual reality based rehabilitation in patients suffering from stroke. Another example of advanced technology use is a study on visual-to-auditory sensory substitution device used by blind subjects (Levy-Tzedek et al., 2012) which helps normal subjects to detect visual stimuli through auditory “music-like” stimulation.

2.2. Neuroimaging

Clearly, clinical studies have benefit hugely from development of non-invasive neuroimaging methods which provide information on brain areas and networks contributing to a given perceptual, cognitive, or motor function. These techniques help to better understand pathophysiology and mechanisms behind treatment-induced functional improvements. A good example is a study conducted by Klingner et al. (2011) showing that transient episode of Bell’s palsy affects fMRI assessed activity and functional connectivity

even after complete clinical recovery. Brain structural alterations were investigated by Li et al. (2013) who showed decrease of gray matter in deaf subjects, and by Rickards et al. (2012) who characterized how structure of the spared neural tissue is related to motor function in stroke patients. In traumatic brain injury patients Bashir et al. (2012) assessed dynamics of functional and structural modifications. Assenza et al. (2013) confirmed prognostic value of EEG recorded in acute stroke patients. Interhemispheric balance was shown to be an important correlate of functional recovery of motor function (Pellegrino et al., 2012, Di Pino et al., 2012) and for recovery in aphasia (Szaflarski et al., 2013), which is in line with preclinical studies reviewed below (Axelson et al., 2013; Sun et al., 2013).

A number of other studies used data acquired with magnetic resonance to investigate auditory perception (Sturm et al., 2011, Jungblut et al., 2012), attention (Clemens et al., 2013), movement execution (Rijntjes et al., 2011; Kimberely & Pickett, 2012, Hassa et al., 2011), and structural features of the brain (Marumoto et al., 2013). Concerning other techniques, Caliandro et al. (2012) investigated the role of prefrontal cortex in control of balance during over-ground ataxic gait using near infrared spectroscopy. Finally, Kotchoubey and Lotze (2013) and Kotchoubey et al. (2013) reviewed neuroimaging and other instrumental methods to diagnose “locked-in syndrome”.

2.3. Non-invasive brain stimulation

Neuroimaging might be complemented by non-invasive neuromodulation techniques, providing opportunity to purposely affect functioning of brain areas, namely excite/inhibit neural tissue, or entrain oscillatory activity. Recently we observed a great increase in the number of studies employing non-invasive brain stimulation (NBS) methods, for instance transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), or transcranial alternating current stimulation (tACS). All the aforementioned techniques provide an opportunity to transiently modulate brain activity and therefore to prove a causal role of particular areas/networks in the process/function under study. Further, existence of protocols inducing long-lasting effects gives researchers and clinicians justified hope to use NBS as a treatment method.

tDCS has been tested as a treatment method for fatigue and sleep disturbances in patients with

polio-syndrome (Acler et al., 2013) and together with occupational therapy in subjects suffering from stroke (Nair et al., 2011; Yang et al., 2012). In aphasia patients tDCS was shown to improve picture naming (Kang et al., 2011) and verb generation (Marangolo et al., 2013). Further, Anastassiou et al. (2013) showed that transpalpebral current stimulation might be a plausible treatment option for patients with age related macular degeneration (AMD). Kimberely et al. (2013) studied whether repetitive sessions of 1Hz TMS might increase cortical inhibition and reduce symptoms of focal hand dystonia.

There are also efforts to check new protocols to increase cortical excitability. Chaieb et al. (2011) tested new protocols which might be used in the future as treatment protocols. Various brain stimulation methods were used to study motor learning (Borich et al., 2011, 2012; Buttkus et al., 2011; Platz et al., 2012a, 2012b) and visual perception (Olma et al., 2011). Turi et al. (2013) studied frequency dependent effects of tACS. Schade et al. (2012) studied effect of handedness on tDCS induced excitability changes. Another study, by showing that movement during tDCS stimulation prevents tDCS-induced plasticity, provided evidence for state-dependency of tDCS effects (Thirugnanasambandam et al., 2011).

Another group of studies combined brain stimulation with neuroimaging in healthy subjects (Antal et al., 2012) and in stroke patients (Chang et al., 2012) to track stimulation-induced changes in functional activation and functional connectivity. Moreover, Allendorfer et al. (2012) showed that anatomical connectivity is altered by repetitive TMS treatment in aphasia patients.

Several reviews relevant to the topic were published covering for instance most recent studies using tDCS (Nitsche & Paulus, 2011), stimulation-induced plasticity in the visual system (Antal et al., 2011). Stimulation in the treatment of aphasia (Chrysikou & Hamilton, 2011; Torres et al., 2013), spatial neglect (Oliveri, 2011), or motor impairments caused by stroke (Hoyer & Celink, 2011) was also reviewed. More generally, usage of stimulation in neurorehabilitation was reviewed by Coslett and Hamilton (2011). Song et al. (2011) reviewed different approaches to modulate somatosensory processing, while Zaghi et al. (2011) conducted a meta-analysis on effects of stimulation used as a treatment in patients suffering from chronic pain. Based on these results, we expect significant developments within this field in the years ahead.

3. Pre-clinical Studies

The picture regarding neuro-restoration and -protection in the area of basic research with animal models looks a bit different compared to the activity in clinical research. We see here a bigger variety within the therapeutic and mechanistic approaches than in the field of human studies – which is actually what one would expect from basic science.

3.1. Stem cells/transplantation

In animal research we see a lot of activity in the area of stem cells and transplantation. This approach is not yet established for clinical therapy; however, a few articles have been published (Bottai et al., 2012; Min et al., 2013; Contreras Lopez et al., 2013; Papadopoulos et al., 2011; Saito et al., 2012). This discrepancy in number of publications is certainly due to the practical and ethical hurdles which need to be considered when going into humans. However, this is exactly the reason why to intensively continue with basic research in this promising area: to develop, to refine, to adjust the treatment and eventually to overcome the hurdles which are currently there. Stem cell/transplantation experiments are performed in various fields, e.g. in ischaemia research. Here results from experiments on stem cells may allow to unfold the restorative potential of these progenitors (Sun et al., 2013), e.g. by rescuing them from apoptosis (Cui et al., 2013). Even more activity in this field has been documented with models of traumatic/nerve injury. A main focus is on methods of transplantation of (peripheral) nerves to facilitate regeneration: neuronal survival, morphology and function can be improved after a lesion with this approach (Chiwitt et al., 2011; Guzen et al., 2012; Lin et al., 2012; Nordblom et al., 2012; Ozsoy et al., 2011). As in the ischaemia field, a closer look at the mechanisms of stem cell proliferation, survival, development and the graft location after trauma or transplantation of precursor cells may open up new ways to foster repair and rehabilitation after nerve injury (Fagerlund et al., 2011; Mohammad-Gharibani et al., 2012; Nandoe Tewarie et al., 2011; Pajenda et al., 2013; Shear et al., 2011; Wallenquist et al., 2012).

3.2. Pharmacology

New and innovative drugs are also a core topic in the animal research field. New hope is raised by

natural compounds, like plant extract bacopaside I and JSK (Liu et al., 2013; Su et al., 2013) against ischaemic or traumatic damage, 4-iodophenol isothiocyanate (Wellejus et al., 2012) to treat M. Parkinson, or tetrahydroxystilbene glucoside (Zhang et al., 2013) against M. Alzheimer.

However, hidden “treatment-treasures” for brain damage and diseases may be also uncovered when taking a closer look at known pharmacological topics: Although having been investigated already for many decades as anti-excitotoxic compounds, antagonists of the glutamate receptors still have not made the transition into a successful therapeutic clinical application. However, a more sophisticated approach, i.e. influencing the glutamate transporters may be a promising way to decrease excitotoxicity and achieve neuroprotection (Beller et al., 2011). Also regarding other known pharmacological approaches further investigations may identify the way to reach neuroprotection: Brendel et al. (2013) showed that especially the estrogen receptor alpha (not beta) mediates anti-apoptotic processes, Menniti et al. (2012) revealed that phosphodiesterase inhibitors may act via peripheral targets. Cekic et al. (2012) showed that Progesterone can improve growth-factor expression profile and the rationale of Progesterone treatment is also strengthened by investigations of further details of the mechanism of action (Morali et al., 2011; 2012; Wang et al., 2013a).

Also so far unutilized opportunities can be revealed by looking closer at the potential of drugs for other indications, for example statins (Chauhan et al., 2011). In the same line, the effects of known drugs / supplements can be optimized (Liu et al., 2012; Wali et al., 2011; Wang et al., 2013c).

3.3. Multi-modal approaches

Multi-target approaches, which are rarely performed in the clinic because of their costs, can, however, show their potential in animal experiments (e.g. growth factors and growth factor releasing hormones; Garcia del Barco et al., 2011, 2013) and, importantly, the benefits of innovative and/or complex treatments (e.g. bone marrow transplantation; gene delivery, biodelivery) can be proven (Meng et al., 2011; Moreno-Igoa et al., 2012; Qinli et al., 2013; Tornoe et al., 2012). The same is true for the treatment with a combination of different drugs: Ozyener et al., (2012) successfully reduced ischaemic damage by a combination of melatonin and

topiramate. Such studies should raise awareness also in the area of clinical research because it can be expected that complex brain pathologies will be only treated effectively by complex, multi-target treatment schedules. For translation into clinic, however, data from the review from Wang et al. (2013b) may also be interesting: these authors found that citicoline, neurotrophin-4 and nitric oxide synthesis inhibitors show the highest effect size in models of traumatic injury.

Going beyond the approach to address multiple targets with the same strategy (e.g. pharmacological treatment), multi-dimensional treatments may be even more promising, which means that authors combine different therapeutical categories. The potency of such approaches (e.g. behavioral training and pharmacology (Sakakima et al., 2012; Wang J et al., 2013a); behavioral training in combination with electrical stimulation (Merceron-Martinez et al., 2013)) can be demonstrated first in animal experiments in order to stimulate also more complex clinical trials.

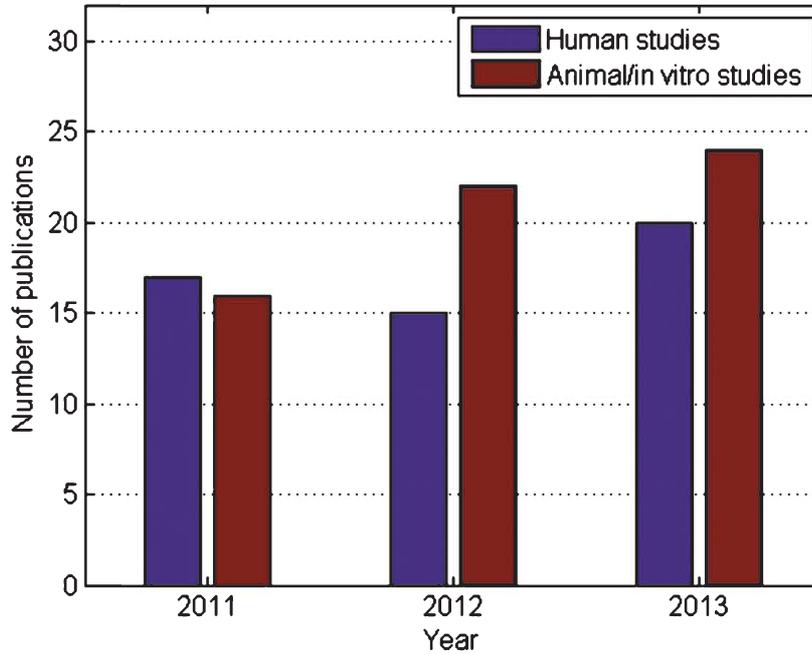
However, to support an unbiased evaluation of such new treatment strategies, RNN also publishes critical results, like ineffective interventions or even detrimental effects of exercises or drugs after traumatic brain injury (Crane et al., 2012; Onifer et al., 2011; von der Haar et al., 2012). These are very interesting data for drawing the attention to the essential details of successful training strategies for motor-rehabilitation, such as the timing: possibly a delayed training schedule is beneficial (Dai et al., 2011).

3.4. Methods

In addition to the studies aiming to induce neuroprotection and/or –rehabilitation, experiments designed for a better understanding of the basic mechanisms behind brain physiology and pathology are a condition sine qua non for progress. To this end, first and foremost, valid and reliable models are of importance for further investigations and are therefore valuable contributions to RNN, e.g. evaluation of species-specific differences (Feeney et al., 2013) or early stages of diseases (Korecka et al., 2013) or developing new or more sophisticated models (Ozsoy et al., 2012; Redondro-Castro et al., 2011; Shahlaie et al., 2013).

A much appreciated development in this respect is that many research projects look at functional outcome. This is true, for example, for pharmacologically enhanced rehabilitation of nerve injuries (Brown et al., 2013; Cekic et al., 2012; Chauhan et al., 2011; Crane

Articles published in RNN per year



Articles published in RNN by categories

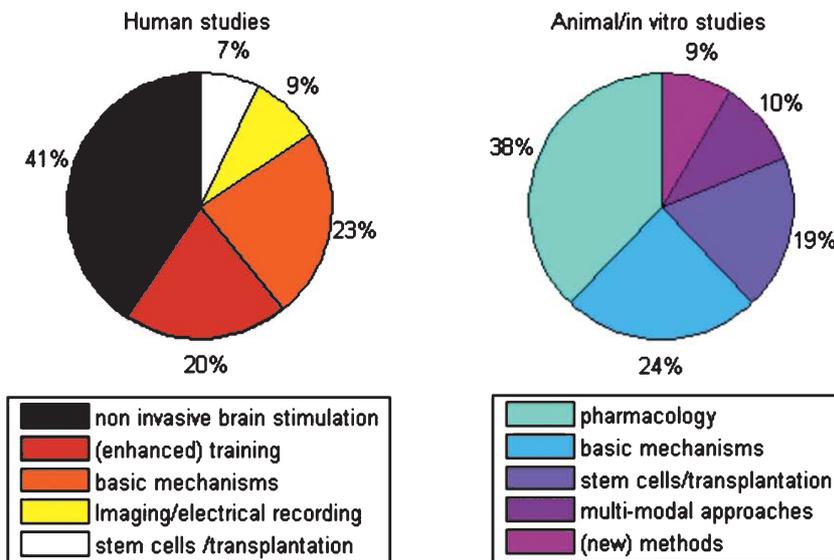


Fig. 1. This figure shows the kind of papers published in RNN in the last few years. We believe that this represents the field of restorative neurology and neuroscience rather well and gives us a sense of priority areas in this field.

et al., 2012; Dai et al., 2011; Guzen et al., 2012; Su et al., 2013).

3.5. Basic mechanisms

Experiments for a basic understanding of mechanisms underlying widely used medications, such as the growth factor-mediated antidepressant effects (Jarosik et al., 2011) are of high interest for science and are therefore welcome by the RNN Editors. The same is true for understanding the mechanisms of endogenous factors of mediating degeneration or regeneration (Jaminet et al., 2013; Keilhoff et al., 2012; Redondo-Castro et al., 2013; Robinson et al., 2013) and for addressing the basic questions about the mechanisms of ageing, like the changes in epigenetic marking of hippocampal DNA (Chen et al., 2012) or the understanding of age-related vision loss (Lehmann et al., 2012).

Another emerging focus of rehabilitation is to take a closer look at the uninjured/contralateral side of the brain after damage, which is in line with a number of aforementioned clinical studies. This includes e.g. plastic changes in the uninjured hemisphere for possible functional rehabilitation of motor function (Axelson et al., 2013). In line with this research are also data indicating an inhibitory influence of the contralateral hemisphere after focal ischaemia (Sun et al., 2012).

4. Outlook

As we see, there was recently a clear focus on (electrical) brain stimulation techniques in the clinical research projects; it seems reasonable to encourage also more basic (animal) research in this area. The relevance of this brain stimulation approach is obvious because of the significant effects already demonstrated in the clinic. A better understanding of the mechanisms, of the treatment protocols and of the side effects is, however, now essential to optimize these procedures. Basic research should be therefore encouraged in this field and with animal models questions regarding (molecular) mechanisms can be addressed to find answers that go beyond what can be investigated in clinical studies. Other areas expected to accelerate in the near future are more refined behavioral training methods and less so new drugs.

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