NEURAL AND BIOCHEMICAL ASPECTS IN REHABILITATION TRAINING

Christian T. Haas and Dietmar Schmidtbleicher

**Institute of Sport Sciences, J.W. Goethe-University Frankfurt
Frankfurt, Germany**

Physiological training is a well known treatment in rehabilitation and prevention. Endurance training programs are used to optimize cardiovascular functions and thereby reduce the risk of heart diseases or stroke; strength training is efficient to avoid or reduce lower back pain or osteoporosis. However, in the last decade strong experimental evidences suggest that training stimuli are also beneficial in the treatment of neurodegenerative diseases (e.g. PD, MS) and neurotraumata (e.g. SCI). At this neurotrophic factors were identified to play a key role. The release function of these substances is highly related to sensory input, especially muscle spindle afferents. As voluntary muscular activation and motor control is impaired in multiple neurological patients and therefore sensory stimulations are reduced, alternative stimulation techniques are of crucial importance. With respect to natural stochastic behavior of nerve cells, neuromuscular activation can be generated using mechanical stochastic resonance (SR) stimulations. These signals are characterized by a coherent wave which is superimposed by noisy influences. Supra-threshold activations result from resonance like behavior between both stochastic signals.

KEY WORDS: stochastic resonance, neuroplasticity, neuroprotection, neurotrophic factors

EXERCISE ENHANCES NEUROPROTECTION POTENTIAL: Exercise is a well known preventive and rehabilitative treatment for several common diseases in modern industrial society. Endurance training was found in multiple experiments to have beneficial effects on the cardiovascular system as well as body composition and thereby reduce the risk of suffering heart diseases, stroke or diabetes. Regular strength training avoids muscle weakness, reduces lower back pain, enhances and improves bone mineral density and structure which helps to reduce the probability of developing osteoporosis.
Extensive research in the last decade shows furthermore that subjects suffering from neurodegenerative diseases, pain, cognitive impairment or neurotraumata benefit from exercise, too (Vaynman & Gomez-Pinilla 2005 for review). Principally these disorders are characterized by different etiologies and pathological structures and a wide variety of mechanisms – like mutant genes, oxidative stress, environmental neurotoxins, DNA or accidental damage etc – are suggested or known to trigger the disease and its progression. However, all of these mechanisms converge on a decline of nerve cells (Mattson & Magnus 2006). Besides disease-specific functions, immobilization and neural inactivity play a key role. In consequence expression of neurotrophic factors – which is fundamentally important for neuronal survival, neurit outgrowth, neuroplasticity and connectivity - is chronically reduced and thereby nerve cells undergo a programmed cell death. As most neurodegenerative diseases like Parkinson's disease, Alzheimer dementia, and diabetic neuropathy occur primarily in elderly subjects, neural vulnerability and cell loss is comparably large as neurogenesis is reduced with ageing.
Extensive knowledge about the functions of neurotrophic factors results from animal models. Mutant animals lacking release capability of neurotrophic factors show characteristic symptoms of neurodegenerative diseases. Thus, Chen and co-workers (2002) found mutant mice ($EG3^{-/-}$), which loose muscle spindle function after birth, developing parkinsonian motor symptoms like ataxia or tremor. The authors argue that peripheral stimuli are drastically reduced and therefore neurotrophic factor release is impaired leading to nerval cell death in the basalganglia. Other researchers worked with neurotoxically lesioned animals. Cortical infusions of neurotoxins (6-OHDA or MPTP) led to strong loss of striatal nerve cells. However, rats that were forced to move or run and to use designated pathological limbs show strongly reduced motor symptoms and furthermore less marked cell death (e.g. Cohen et al. 2003, Tillerson et al. 2002). The authors argue that training stimuli lead to a marked

expression of neurotrophic factors that reduce striatal cell vulnerability and cell loss. However, neurotrophic factor release seems not to respond to movement per se. Experiments of Hutchinson et al. (2004) and Gomez-Pinilla et al. (2002) – focusing the possibilities of nerve regeneration in spinal cord injury – show a tendency that the release function is connected with movement velocity. Standing does not lead to neurotrophic factor release and swimming results only in very moderate expressions. In contrast running was found to be highly effective for neurotrophic factor expression. However, multiple neurological patients are not capable to exercise voluntary (e.g. running) and therefore ballistic sensory stimulation are missing and potentially expression of neurotrophic factors is not sufficient to avoid further disease progression or promote neurit outgrowth and nerval regeneration. Consequently, one might bypass voluntary activation cycles and simulate sensory stimuli, especially eliciting muscle spindle afferents. Similarly, huge mechanical strain should not occur as the neuromuscular system is usually not prepared adequately in these patients and fractures or other lesions might result.

STOCHASTIC RESONANCE: With respect to a natural intrinsic stochastic behavior of nerve cells, oscillatory stimulations superimposed by random noise – termed Stochastic Resonance – show huge conformity with the requirements presented above. Stochastic Resonance (SR) is a phenomenon found in many nonlinear dynamic systems (Gammaitoni et al. 1998 for review). The basic functions are very robust and mathematically present- and provable. In the most general form it is characterized by a form of threshold or barrier and two or more inputs. Generally one input is a coherent signal; another input of the same modality is random and/or stochastic noise.
Referring to the noisy behaviour of nerve cells stochastic components of SR generate a resonance like behavior which enable supra-threshold activations using weak mechanical stimuli. „Noise thus could play a major role in signal processing by CNS neurons, both in slices and in vivo“ (Stacy & Durand 2000, 1401). With respect to neurotrophic factors a 10-fold larger release became evident using stochastically superimposed theta waves compared to sinus signals of the same basic frequency (Balkowiec & Katz 2002).

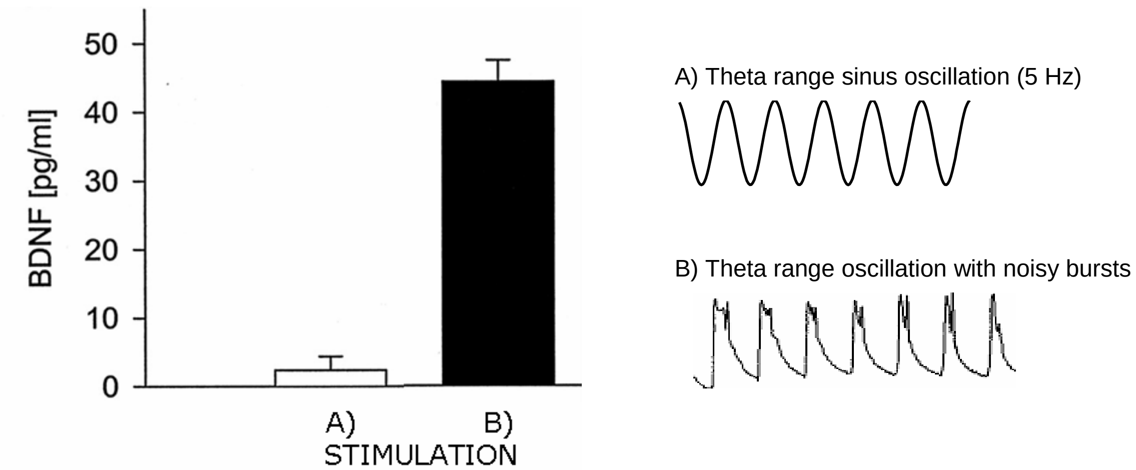

Figure 1: Expression of brain derived neurotrophic factors (BDNF) in vitro (adapted from Balkowiec & Katz 2002). Compared to harmonic sinus stimulation, noisy influences within the same basic frequency lead to a 10-fold enhanced neurotrophic factor release.

However, even if SR functions can be identified in single nerve cells and on molecular level, it can furthermore influence signalling in complex neural networks and thereby sensorimotor control. Each type of control mechanisms requires a certain content of information. In motor control information about environmental conditions and limb positions are necessary to enable adequate decision taking. Information processing is strongly connected with signal detection capability. However, this ability is frequently impaired in neurological patients (e.g. PD, stroke, neuropathy) and therefore mechanisms that enable sensitive and early detection of external stimuli is of primary importance. If one lacks adequate information about environment conditions context adapted movement selection capability is reduced. A couple of studies found that adding appropriate levels of stochastic influences in stimulating signals (SR) enhance their detectability. “Stochastic resonance (SR) is a nonlinear cooperative effect wherein the addition of a random process, or ‘noise’ to a weak signal, or stimulus results in improved delectability or enhanced information content in some response” (Ward et al. 2002 91). Thus, Liu and co-workers (2002) found 34% better detection of SR signals compared to sinus waves in neuropathic patients. Wells et al. (2005) and Khaodhiar et al. (2003) show similar results in young, elderly and neuropathic subjects. However, functions of SR are not limited to sensory processing only. In various experiments it became evident that mechanical stimulation superimposed with random and stochastic components can reduce symptoms and optimize motor control in neurodegenerative and movement disorders patients (Haas et al. 2006, Turbanski et al. 2005, Schuhfried et al. 2005).

Exemplarily, figure 2 shows the results of a long term single case study. Three to five stochastic resonance training sessions were applied each week to a MS patient. Huge postural control improvements became evident spontaneously (i.e. after each trainings session) as well as in the further course of the experiment. As these changes represent a single case only, they might not be regarded being totally representative. However, Schuhfried et al. (2005) and Turbanski et al. (2005) found similar postural control effects of SR training in MS and PD patients.

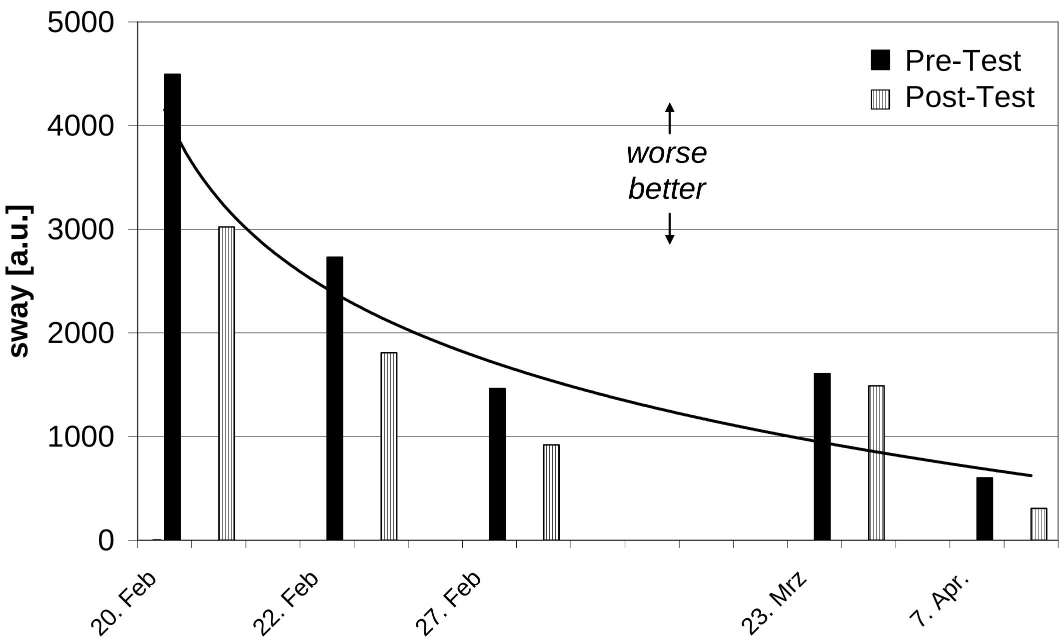

Figure 2: Postural control changes of a MS patient during a stochastic resonance training experiment.

Referring to other experiments one might explain these effects through neurotransmitter releases and signal processing changes in the basalganglia and in prefrontal areas (Haas et al. 2006). From another point of view it seems also plausible that the noisy part of SR implies continuously new sensory weightening which improves information selection and Maximum-Likelihood-Estimation of efferent commands (Halford et al. 1998). „In other words, increasing noise (increasing disorder) in the input may result in increasing order in the output. This seemly striking feature of nonlinear stochastic systems is termed as stochastic resonance (SR)” (Xiao 1998, 133).

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