"Vibratory Stimulation and Stochastic Resonance Therapy: Results from studies in Parkinson’s disease and spinal cord injury"

Christian T. Haas
Goethe-University Frankfurt, Institute of Sport Sciences,
Ginnheimer Landstr. 39.
60487 Frankfurt, Germany
c.haas@sport.uni-frankfurt.de

Abstract. Locomotion training has been found being effective in various fields of rehabilitation. Besides improving locomotion performance and mobility it became evident in Parkinson’s disease (PD) animal experiments that regular locomotion exercises (or forced use strategies) are associated with neuroprotective effects in multiple brain areas. However, numerous neurological patients are unable to do locomotion exercises - by coordinative or energetic reasons - and therefore rehabilitative potentials are reduced. We try to bypass this gap using vibratory stimulations, leading to reflex answers similar to reflex elicitations during human locomotion. Referring to simulations in artificial neural networks and information processing experiments, stimulating signals are superimposed by stochastic components which facilitate nerve threshold crossing and enhance neuromuscular activity. In studies with PD and spinal-cord-injury patients we found that regular stimulation series lead to significantly improved postural control and locomotion abilities. Interestingly, PD patients show also reduced symptoms (e.g. tremor, rigidity) in the upper extremities.

Keywords: Parkinson’s disease, spinal cord injury, rehabilitation, vibration, stochastic resonance

1 Introduction: Therapeutic effects of running movements – results from animal studies

The ability to walk and moreover to run is fundamentally connected with humans’ evolution. Since thousands of years walking is the key component of humans’ mobility and running ensured survival as it enabled us to flight in case of danger. Thus, it is not surprising that walking or running movements and elementary functions of the nervous system (e.g. neuroplasticity, nerve growth, neuroprotection) influence each other: Alaei and colleagues [1] showed in an animal experiment that treadmill running significantly enhanced mid-term memory. Van Praag and co-
workers [2] found running exercise increasing cell proliferation and neurogenesis in
the hippocampal area statistically stronger than other training exercises like
swimming or water maze learning. The authors argue that running movements
generate strong neural theta-band\(^1\) activity which interferes with the intrinsic theta-
activity of hippocampal nerve cells and thereby enhance total theta-range firing. This
neural activity pattern is suggested being responsible for neurotrophic factor releases
which enhance nerve growth via molecular pathways. In concordance with this
functionality electrical theta-burst stimulations of neural networks were found leading
to maximized neurotrophic factor releases and neuroplasticity, respectively [3].

Hutchinson and colleagues [4] proved the effects of different exercises referring to
biochemical reactions and behaviour: They found running exercise leading to stronger
neurotrophic factors releases than swim- or stand-training. Furthermore, it became
evident that pathological painful sensations (neuropathic pain) are fundamentally
lower after running compared to the other exercises. It is likely that both processes are
functionally connected. Thus, a higher release of neurotrophic factors avoids or
reduces death of (sensory) nerve cells and avoids or reduces developing pathological
neural network dynamics. Ying et al. [5] found a strong positive correlation between
the running distance per day and the release of BDNF (brain derived neurotrophic
factors) and Molteni and co-workers [6] identified that running distance and nerve
growth are correlated positively highly. Furthermore, in several Parkinson’s disease
(PD) animal experiments it became evident that forced use of extremities and forced
running, respectively, leads to less degeneration of the dopaminergic nervous system
and furthermore to less marked parkinsonian motor symptoms [7, 8]. By contrast,
forced non use conditions promoted the intense of PD symptoms.

In summary, multiple well controlled animal studies found that running exercise is
connected with a functional circle of enhanced neurotrophic factor release, enhanced
nerve growth and regeneration, reduced nervous degeneration and fewer symptoms.

However, numerous patients are unable – by energetic reasons or coordinative
deficits – to realize walking or running exercises. Consequently, rehabilitative
potentials are reduced in these subjects. We try to counteract this problem using
external mechanical (vibratory) stimulations. This technology can be used to bypass
voluntary muscular activation deficits via eliciting neuromuscular stretch reflexes [9-
11]. As similar reflex patterns can be identified during running one can speculate
about further beneficial effects of vibratory stimulations.

Principally literature shows a wide variety of vibration induced physiological
effects and furthermore strong influence of vibration parameters like frequency,
amplitude, stochasticity etc. [9-12]. In order to clarify this structure the following
chapter wants to give a short overview about physiological and biomechanical
reactions of vibratory stimulations.

\(^1\) The theta band ranges from 4 – 8 Hz.
2 Effects of vibratory stimulations in humans

The use of vibration in neurorehabilitation is already described in the 19th century by the French neurophysiologist Jean-Marie Charcot. He found that vibratory stimuli reduce symptoms of Parkinson’s disease patients or subjects suffering from the Tourett-Syndrome [13-14]. In the 20th century systematic analyses were realized by Coermann [15-16] and later by Diekmann [17-19]. Their research focused on one hand on establishing stimuli-response principles. On the other hand they tried to identify vibratory risk factors and to develop preventive strategies. In 1966 Matthews [20] as well as Hagbarth und Eklund [21] described a phenomenon (Tonic-Vibration Reflex (TVR)) which became fundamental important for decades of future research. The TVR is a reflectory muscular activation resulting from a transfer of vibrations to the muscular tendon system which is accompanied by repetitive muscle spindle stretches. Further studies showed that „This tonic vibration reflex (TVR) […] varied in strength from one subject to the next“ [22, p. 719]. This finding might also explain the wide heterogeneity of study results in the field of vibration research, reaching from risky to highly beneficial [9-12]. The nonlinear stimulus response reaction is even fundamentally determined by physical functions. Thus, men represent a multi level, mass- and spring-coupled oscillatory system working as a frequency-sensitive filter. Both, the filter type (low-pass or high-pass) as well as the cut of frequency of the filter can vary depending on the transfer location of the stimulus, subject’s posture, muscular stiffness etc. As a result vibratory stimuli might impact on the muscles (e.g. m. quadriceps) interindividually differently, even if the input vibration (e.g. at the feet) is the same in two subjects. The nonlinear functioning of the system results furthermore from a quick changeability of the muscular-tendon stiffness (via gamma-innervations) which affects in a further step the natural frequency of the system and resonance phenomena. Even changes in the local blood flow can influence natural system frequency and resonance generation as the mass of organs – which behave like oscillators – is modified.

Besides these physical functions the system complexity is also influenced by physiological functions. Thus, detection and integration of vibratory stimulations is not only based on a single receptor type (e.g. muscle-splindles). Various other receptors like the golgi-tendon organ or cutaneous receptors etc. are sensitive for vibratory stimuli and it is likely that – except artificial laboratory settings – a multivariate sensory processing dominates. Referring to biochemistry McCall and co-authors [23] found interesting reactions that illustrate again the nonlinear system behavior: While applying vibration to the m. tibialis anterior increased concentration of BGH (bioassayable growth hormone) of about 94% could be identified. By contrast vibrating the antagonist resulted in a decrease of about 22%.

With respect to the complex interaction of vibration and physiological reaction it is not surprising that vibratory stimuli can also disturb motor control or even generate pathologies. For instance loss of sensation and decrease of blood flow (vibration white hand / feet syndrome) can be the consequence of transferring high frequent vibration chronically to the extremities (hand or feet). This happens frequently when
workers use vibrating tools or stand repeatedly and for long duration on vibrating platforms [24-27].

Non chronic vibratory induced motor control disturbance are also well analyzed and described in literature. Commonly “kinaesthetic illusions” are fundamentally responsible for this kind of motor control dysfunctioning. Muscle spindle afferents are important sources to control joint angles and to organize spatial orientation. When high frequent vibrations are transferred to the muscle spindle, afferents encode information about two aspects: current joint angle (quasi static information) and repetitive muscle stretch (dynamic information). However, both information sources cannot be separated and the repetitive, vibratory induced muscle stretch is interpreted – by the reason of its high vibration frequency – as a constant stretch. This leads to continuous miscoding, i.e. wrong information about the current joint angles. Verschueren et al. and Ivanenko et al. [28-33] showed in multiple experiments that kinaesthetic illusions can disturb manual coordination as well as locomotor activity or postural control.

In summary vibration affects various physiological functions on different levels in a highly nonlinear way. Thus, small variation of stimulation parameters can result in a totally different reaction. Consequently, we should not put the light on generating involuntary muscular activation via eliciting reflex answers, only. Concurrently, bypassing voluntary muscular activation deficits via vibratory stimulation shows great potentials in the field of rehabilitation. In order to improve and train signal-detection and weightening of different sensory afferents it seems useful to avoid strong harmonic stimulation forms, i.e. implementing random and stochastic influences improve sensory processing and adaptation of the sensorimotor system. Experiments in the field of Stochastic Resonance (SR) research provide the basis for these principals.

3 Stochastic Resonance: Principals and basic functions in biological systems

Stochastic Resonance (SR) is a phenomenon found in many nonlinear dynamic systems, including the nervous system (Gammaitoni et al. 1998 for review). It was firstly proposed by Benzi in the 1980s who described and explained periodic climatic changes of ice ages [35-36]. In the last decade SR has attracted considerable attention in the field of neuroscience. The basic functions are very robust and mathematically provable. In the most general form SR is characterized by a type 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. Linking to neuroscience arose from a natural stochastic spiking behaviour of nerve cells [37-39]. This is on one hand generated intrinsically - by membrane properties and other cellular mechanism - to promote neural development. On the other hand it results from a synaptic bombardment within the nerval network. Due to this stochastic function, noisy stimulations undergo a resonance like behaviour, i.e. stimuli are amplified and can
become supra-threshold relatively easy. Figure 1 shows the effects of two different stimuli (sinus-wave vs. stochastic resonance signal) in a simple nerve cell model. Even if the average amplitudes of both signals are identical only SR stimuli become supra-threshold. In humans the process of reaching supra-threshold activation is the neural basis of perception or muscular contraction. Referring to rehabilitation the function to generate muscular activation via weak mechanical signals is of fundamental importance as multiple subjects are not prepared for huge mechanical loading and similarly they show impaired ability to contract muscles voluntarily.

![Figure 1: Simulation of synaptic activity and spiking behaviour in a simple nerve cell model. While sinus stimulation leads to synaptic nerve cell activity below the threshold (○), SR generates supra-threshold activity (▲) which is connected with action potential spikes.](image)

Besides simulations in artificial models, several human studies confirm that signal detection and integration can be improved if appropriate levels of stochastic influences were added to the stimulating signal. Thus, Liu and co-workers [40] found 34% better detection of SR signals compared to sinus waves in neuropathic patients. Wells et al. and Khadghi et al. [41-42] show similar results in young, elderly and neuropathic subjects. However, functions of SR are not limited to sensory processing only. There is good evidence that stochastic resonance like effects might also structure complex control processes in humans.
4 Effects of vibration and Stochastic Resonance stimulation in neurorehabilitation

The consequences of neural injury (e.g. spinal cord injury) or neurodegenerative disorders (e.g. Parkinson’s disease) are not just a break in communication between neurons, but a cascade of events occur that promote further neuronal degeneration, cell death and motor dysfunctioning [43]. As argued above mechanical stimulations might be a useful method to counteract neural degeneration and to promote regenerative processes. We proved this hypothesis in multiple experiments with subjects suffering from neurodegenerative and -traumatic disorders.

Referring to Parkinson’s disease various experiments are conducted using vibratory stimuli. However, most studies used vibrations for diagnostic reasons, i.e. to analyze proprioceptive performance and sensory processing respectively [43-44]. By contrast Jöbges et al. [46] proved therapeutic potentials of vibrations. They transferred high frequent vibrations on arm muscles of PD patients. It became thereby evident that the tremor amplitude was lowered when stimulation started. However, when vibration transfer was stopped, the tremor intensity re-established again. The authors speculate on one hand about damping the tremor amplitude via spinal reflex pathways. On the other hand resetting of hyper-synchronized neural tremor-oscillations – generated by vibratory induced afferents – is discussed.

In own studies it was also found that vibratory stimulations can reduce tremor oscillations in PD. Though, in this experiment the effects were analysed before and after applying 5 series of mechanical whole body stimulations taking 60 seconds each. Vibration amplitude was 3mm; the mean frequency was set at 6 Hz and – with respect to theoretical considerations – superimposed by random and stochastic influences. Using the UPDRS motor score (Unified Parkinson’s disease Rating Scale) in overall 68 PD patients tremor scores were reduced on average by 25% and rigidity by 24% [9, 47]. Except cranial symptoms all other symptom groups (tremor, rigidity, bradykinesia, gait and posture) improved highly significantly. As improvements in manual coordination (e.g. writing performance, figure 2) were confirmed in further standardised experimental setting it seems unlikely that this vibratory stimulation affects only the muscle or exclusively the peripheral nervous system.

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2 The author wishes to thank Nadine Scholl, Stephi Kersten and Bastian Scheu for their assistance during spinal cord injury research projects.
Pre-Test

Figure 2: Changes in writing performance before (upper example) and after (lower example) applying 5 series of mechanical whole body stimulation in a PD patient. Complete data show reproducible and significantly improved performance in most patients. Though, performance change in this example is very obvious compared to other improvements.

By contrast one can speculate about surraspinal phasic dopamine releases [9, 47]. This seems a possible reaction since dopamine neurons are highly sensitive for novel situations and unpredictable stimuli – which we used in our experiment. Results of Nelson and colleagues [48] support these theoretical considerations. They found that stimulations via mechanical random waves increase activity of cortical areas (e.g. prefrontal areas, supplementary motor area (SMA)) significantly stronger than sinus waves. As there are strong projections from the basal ganglia to these cortical areas a functional interaction is likely, i.e. dopaminergic reactions could present the basis for changes of cortical activity. Increasing activity in the SMA or in prefrontal areas via external stimulation is of special importance for PD since these areas are frequently hypoactive, being responsible for various motor dysfunctioning [9, 47].

From a clinical point of view vibration induced improvements in postural control (compare figure 3) are more important as disturbances in this field cannot be treated effectively by pharmaceutical interventions [9, 49]. However, it is necessary to mention that the degree of postural control improvement depends on one hand on the testing conditions (e.g. static vs. dynamic) and on the other hand on the symptom
characteristics (highly vs. lowly impaired) and pharmaceutical influence (on vs. off L-Dopa) [49, 50].

Figure 3: Examples of dynamic postural control tests (anterior-posterior sway) pre and post applying 5 series of mechanical whole body stimulation in a PD patient. The effects were proved in different experimental settings (dynamic vs. static test, different positions, ballistic perturbation, “on” and “off” medication). Most analyses show significant improvements of postural control compared to control conditions [9, 49].

As explained above endogenous dopamine releases - resulting from unpredictable stimulations - could explain motor improvements in PD. Nevertheless, patients suffering from multiple sclerosis show also improved postural control performance after these types of mechanical stimulations [9, 51-52]. Therefore – besides dopaminergic reactions – physiological changes on multiple levels are likely. Studies with spinal-cord-injury (SCI) patients confirm this speculation. Changes in reflex pattern were proved in complete SCI patients during mechanical stimulations using a similar experimental setup as explained above. However, as patients were unable to stand they were placed on a chair and both legs were connected with two independently oscillating platforms. Figure 3 shows muscular reflex answers (m. gastrocnemius lateralis) resulting from repetitive and ballistic spindle stretches during stimulation. At the beginning of the training a moderate reflex intensity could be identified. Conversely, after a few weeks of training (3 training sessions / week with 10 series each session) a strong and more complex reflex answer became evident. In some individuals the strength of reflex activity increased by >300%. As similarly reduced spasticity was found we suggest that these adaptations result from a restructured neural network which is in turn highly related to neurotrophic factor release.
Figure 4: Example of muscular reflex pattern (EMG of m. gastrocnemius lateralis) of a SCI patient during mechanical SR stimulations. In an early phase (left) the intensity of reflex activity is low and the pattern is characterized merely by single spikes. After 12 weeks of training (3 sessions / week) the reflex pattern becomes more complex, structured by multiple spikes, and more intensive. As spasticity of the patient was similarly reduced, changes in reflex activity can only be explained by restructuring of the peripheral neural network.

Pearson [63] speculates that enhanced reflex function could contribute to improve locomotion ability after moderate spinal lesions. Consequently we proved the effects of mechanical SR stimulation in multiple incomplete SCI patients. All subjects were out of acute phase (> 24 month after injury), i.e. potential beneficial effects in these chronic patients cannot be explained by spontaneous healing phenomena. After 8 weeks of training (3 sessions / week) improved locomotion performance could be identified in all subjects. Exemplarily figure 5 shows data of two individuals in the ‘get up and go test’. In both cases clear improvements can be identified.

Figure 5: Performance of incomplete SCI patients in the ‘get up and go test’. In both subjects walking performance improved strongly after 8 weeks of SR training.
Figure 6: Vertical ground reaction forces of an incomplete SCI patient during a treadmill walking test. In the pre-test dominant use of one leg became evident. After 8 weeks SR training (3 sessions / week) force curves of right and left leg were similar and the stride frequency increased, representing a better locomotor performance.

Interestingly these changes in walking performance are mostly connected with modified coordinative patterns. Thus, figure 6 shows data of a dynamometric walking test using a treadmill. In the pre-tests a clear unilateral loading became evident which represents on one hand a pathological walking pattern. On the other hand chronic unilateral loading is frequently accompanied with enhanced risk of falling, suffering hip- and knee-arthritis and lower back pain. In the post-test a balanced loading between right and left legs as well as a higher cadence could be identified. Especially the last phenomenon became evident in nearly all subjects.

Referring to neuromuscular activity figure 7 shows exemplarily changes in EMG pattern. In the pre-test a co-contraction between m. gastrocnemius and m. tibialis anterior could be identified during the stance phase which is – from an energetic point of view – non-useful. Furthermore the co-contraction represents fundamental motor control deficits. The patient tries to compensate coordinative deficits via a tonic ankle fixation that reduces degrees of freedom and information processing load. In the post-test the patients has learned to switch between agonist and antagonist activation. This enables on one hand a higher stepping cadence and on the other hand a more economical walking. As analogical improvements could be identified in multiple patients one should discuss transfers and interaction between mechanical stimulation and adaptations in walking pattern.
Figure 7: Vertical ground reaction forces, EMG pattern of m. gastrocnemius and m. tibialis anterior during treadmill walking test. In the pre-test a low cadence as well as a co-contraction between m. gastrocnemius and m. tibialis anterior is obvious. After 8 weeks of SR training (3 sessions / week) a higher cadence and no co-contraction – in contrary timed switching between m. gastrocnemius and m. tibialis anterior activation – became evident.

When we look at robotic engineering it becomes easily obvious that walking is a highly complex movement. Various joints are functionally connected uni- and contralaterally. Thus, walking subjects have to control multiple degrees of freedom which is – from an information theoretical point of view – accompanied with huge processing load. If external demands are high information processing might collapse. In order to reduce control demands and processing loads subjects take out degrees of freedom via tonic fixation of joints. This phenomenon becomes – among others – obvious in movement disorders or in the initial phase of motor learning processes.
As described above the stimulus we used is on one hand superimposed by stochastic influences. One the other hand the basic signal contains also random components. Thereby, it becomes necessary to weighten and select sensory afferents continuously newly in order to generate effective efferent commands. One can speculate that this procedure trains – via processes like Maximum-Likelihood-Estimation and self optimisation – to build conceptual chunks and functional units, respectively [53-54]. In consequence, one has to control only the chunks/units and not their constitutive components as they are trained to interact autarchically. Overall this process is accompanied with reduced control demands and free information processing resources. However, a precondition of this kind of functioning is a transferability from SR-stimulation related training- and learning-effects to walking. Currently, we cannot give clear empirical proof on this concept but analogical functions are described in the field of synergetic, system dynamics information theory and differential learning. Xiao et al. argue similarly „[…] 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)” [55, p. 133]. Anyway, even if we can only speculate about changes in the nervous we can measure the outcome referring motor control. Luckily results are frequently beneficial.

5 Concluding remarks

As shown above locomotor activity (walking, running) can play a fundamental role in neurorehabilitation and also enriched environmental conditions are found increasing neurotrophic factor release and neuroplasticity. Stochastic Resonance was shown being a mathematically provable concept which is used to explain phenomena in different scientific fields. With respect to neurorehabilitation SR function might work as a connecting link between exercise physiology, neuropsychology, animal experiments, electrophysiological stimulation experiments (e.g. theta-burst stimulation) etc. However, even if SR would only be responsible for changes in the excitability of neurons Destexhe and Marder [56] argue that this phenomenon can also trigger neuroplasticity. Thus, Fallon and co-workers [57-58] showed that cutaneous and especially muscle receptors are highly sensitive for noisy superimposed stimuli. As shown above activation of these sensors is connected with neurotrophic factor releases and neuroplasticity. A functional connection between SR and neurotrophic factor release seems to make sense also from an evolutionary point of view. The more variable or noisy environmental conditions are the more neuroplasticity is necessary – which depends on neurotrophic factor release – to

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The difference between stochasticity and randomness is explained and discussed in the article of Davids et al. "Essential noise" - enhancing variability of informational constraints benefits movement control: a comment on Waddington and Adams (2003) [64].
enable quick and adequate motor control and cognitive adaptation. Furthermore, Balkowiec and Katz [3] showed in an in-vitro experiment that electrical sinus stimulation of nerve cells leads to low or moderate BDNF releases, whereas theta-burst-stimulations (these signals are characterized by coloured noisy components) generate the highest release - up to 10-fold higher - compared to theta range sinus wave stimulation.

However, besides SR related phenomena, exercise alone was also found having fundamental importance for neurotrophic factor release and neurorehabilitation. This function becomes more important as external administration of neurotrophins is difficult by the reason of large molecules which can cross the blood brain barrier only to a low extent. Furthermore external administered neurotrophins might diffuse unspecifically without reaching the target neurons and high doses promote the risk of suffering from epilepsy [59-62].

References


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