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Cognitive Recovery and Rehabilitation After Brain Injury: Mechanisms, Challenges and Support

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1. Introduction

When the brain is injured by vascular incidents (stroke) or mechanical impact leading to traumatic brain injury (TBI), the consequences for the patient are almost inevitably impairments within the motor, sensory, and/or cognitive domains. Such impairments may initially appear more disturbing and devastating to the patient – as well as to her/his loved ones – if the motor abilities are affected. The future of the patients in terms of quality of life, ability to return to independent living and potentially work may, however, depend more crucially on the degree to which the cerebral injury has caused impairments within cognitive domains such as language, attention, learning, memory, and problem solving (e.g. Moore & Stambrook, 1995). In spite of the devastating impact cognitive impairments frequently have on the future life of brain injured patients, there has historically been a disproportional focus of both research and therapeutic efforts on the motor symptoms. While research and therapeutic development within the motor domains are still in need of greater efforts, there is an even more compelling need for such efforts within the area of cognitive consequences of brain injury.

2. Cognitive recovery after brain injury

When injury severs the input or output pathways of the brain (e.g. the optic nerve or the major descending motor pathways) the consequences may be a rather chronic loss of sensory input or the ability to execute motor action, respectively. In such cases the degree of posttraumatic functional recovery may remain limited although processes of an obviously "compensational" nature may allow the patient to achieve at least some degree of "recovery". In case of the complete loss of sensory input within one modality, a degree of intermodal plasticity may allow input via other modalities to substitute somewhat for the lost input (e.g. Bach-y-Rita et al., 1969, 1998; Kaczmarek et al., 1991; Ptito et al., 2005). And spared parts of the motor output pathways may allow the patient to achieve at least some level of mobility (e.g. Levin et al., 2009). Within the cognitive domains, however, a certain level of posttraumatic functional recovery and clinical rehabilitation appears to be more the rule than the exception.

When posttraumatic functional recovery is defined as a more or less complete return to the pretraumatic level of behavioural/cognitive proficiency of task performance and/or conscious representation, such a recovery is documented in numerous studies in both patients and animal models (e.g. Buller & Hardcastle, 2000; Carney et al., 1999; León-Carrión & Machuca-Murga, 2001; Mogensen, 2011a, 2011b, 2011c; Mogensen & Malá, 2009; Mogensen et al., 2004a, 2007; Overgaard & Mogensen, 2011; J. Panksepp & J.B. Panksepp, 2000; Ramachandran & Blakeslee, 1998; Rohling et al., 2009). Mostly, such instances of posttraumatic functional recovery are demonstrated in association with formalized rehabilitative training. There are, however, also instances of what is termed "spontaneous" recovery (e.g. León-Carrión & Machuca-Murga, 2001). A recovery process is normally defined as being "spontaneous" if the subjects – patients or experimental animals – have not been subjected to a specific posttraumatic training procedure, and it is frequently implied that the "spontaneous" recovery is the result of one or another type of experience-independent process. It may, however, be naïve automatically to assume that recovery in the absence of formalized training is necessarily experience-independent. Even in the absence of formalized training, patients and experimental animals alike are constantly exposed to the challenges of daily living. Under almost all circumstances, daily activities such as (more or less successful) coordination of movements, communication (or attempted communication), feeding and other basic activities constitute in themselves informal types of "training". Consequently, it is hard to discriminate between experience-dependent and experience-independent types of recovery processes. There can, however, be no doubt that truly experience-independent processes do occur. One example is recovery associated with disappearance of an injury-associated "penumbra". Briefly described, the penumbra phenomenon is a situation in which injury within one part of the brain causes other brain areas to receive a reduced level of blood supply. Although the reduced blood supply within the penumbra region is sufficient for the survival of the neurons, normal levels of functionality are not possible within the tissue affected by the penumbra. Consequently, the symptoms observed during the presence of the penumbra are a combination of the consequences of the actually lost tissue and the functional impairments within the brain regions affected by the penumbra. Penumbras mostly disappear spontaneously and when that happens, a normal level of functional performance is restored within the affected part of the brain (e.g. Choi et al., 2007).

Both clinically and in animal models the degree to which the functional recovery manages to eliminate the trauma-associated symptoms varies greatly. In some instances, even extensive rehabilitative training can only achieve limited degrees of functional recovery, while in other instances the recovery turn out to be "complete" – when defined as the acquisition of a posttraumatic proficiency equal to that seen in the absence of any brain injury (e.g. Mogensen et al., 2004a). It is important to stress that in animal models such a "complete" functional recovery can be demonstrated even under circumstances ensuring the complete removal of the brain structure in question – and utilizing comparisons to a well-established pretraumatic functional baseline. From a theoretical point of view such a functional recovery – but for the few instances in which it may be ascribed to the disappearance of penumbras or similar phenomena – poses a severe challenge to the concept of "functional localization".

2.1 Functional localization and recovery

Within the neuroscientific literature there is a widespread consensus that a regional specialization exists within the brain. Various structures and substructures are functionally

specialized and it appears to make sense to speak about a "localization" of various "functions" (e.g. Coltheart, 2001; Kringelbach & Rolls, 2004; Monakow, 1914; Selnes, 2001). Support for the idea of a functional specialization within the structures of the brain mainly comes from two sources: (1) various types of neuroimaging techniques (e.g. PET and fMRI) reveal rather consistent patterns of regional cerebral activation when subjects are stimulated in particular ways, perform particular tasks, etc., and (2) "lesion experiments" (be it clinical examinations of brain injured patients or controlled experiments in animal models) demonstrate that lesions or regional inactivations within a particular brain structure are associated with specific patterns of symptoms.

Especially the latter source of evidence for a functional localization is directly related to the mentioned contradiction between "functional localization" and posttraumatic "functional recovery". While it seems logical that loss (lesion) of a specialized brain structure leads to a predictable type of impairment (reflecting the posttraumatic absence of that functional contribution) it appears illogical to expect a "recovery" of the lost "function" after lesions of a specialized brain structure – since regrowth of the missing brain region appears not to occur. Nevertheless, localization as well as posttraumatic recovery of functions are highly documented empirical facts (see above and e.g. Mogensen, 2011a, 2011c; Mogensen & Malá, 2009). To resolve this apparent contradiction is not only an important theoretical challenge in order to understand the functional organization and reorganization of the brain. It is also an important issue in the context of developing new clinical methods aiming at improving, supporting and completing the rehabilitative efforts within cognitive domains.

Aphasia may be one of the best-studied clinical conditions when it comes to the attempted mapping of the neural substrate of functional recovery. Aphasias primarily result from injury to the left hemisphere, and ipsilateral contributions to the mediation of reacquired linguistic functions have been documented by for instance Szaflarski et al. (2011), Perani et al. (2003), Specht et al. (2009), and Meinzer et al. (2008). Meinzer et al. (2008) demonstrated treatment-induced reintegration of various perilesional areas. However, the most commonly asked question in the field of posttraumatic reacquisition of language is, whether the contralateral (right) hemisphere contributes significantly to the mediation of posttraumatic recovery? Numerous studies have found the apparent involvement of structures within the right hemisphere in the mediation of posttraumatic recovery of language (e.g. Ansaldo & Arguin, 2003; Ansaldo et al., 2002; Baumgaertner et al., 2005; Perani et al., 2003; Specht et al., 2009; Thomas et al., 1997; Thulborn et al., 1999). There are indications (e.g. Thomas et al., 1997) that the pattern of shift towards right hemisphere mediation of linguistic functions may differ between types of aphasia. Additionally, changes in the direction of right hemisphere mediation of language may be accompanied by internal reorganizations within the left hemisphere (shifts to ipsilateral mediation by uninjured regions). These reorganizations may lead to a more bilateral representation of language – due to the concurrent shift of linguistic mediation within the left hemisphere and to the contralateral, right hemisphere (e.g. Thompson et al., 2010). Mostly, the recovery-associated shifts towards right hemisphere mediation of linguistic functions seem to occur without rehabilitative training specifically aimed at such a shift (instead, rehabilitation has been aimed in a more general way towards recovery of linguistic abilities). However, in some cases aphasic patients have – somewhat successfully – been subjected to training aimed at achieving a higher degree of right hemisphere mediation of linguistic tasks (e.g. Crosson et al., 2009). Crosson et al. (2009) used a manipulation task performed with the patient's left hand to initiate naming trials and thereby obtain an independent right hemisphere activation, which presumably can ease an

interhemispheric shift of linguistic task mediation. It may be questioned to what extent the changes in neural activity observed via for instance fMRI in a recovering or recovered aphasic patient are specifically related to the reacquisition of language. Posttraumatic changes in activity within a given structure may be the consequences of any trauma-related process – e.g. "disinhibition" due to lack of input from the injured brain region. Or for that matter any other process, which is not directly related to the recovery of linguistic abilities. Such reservations may be less prominent in certain cases. For instance, Meinzer et al. (2007) studied the recovery of a bilingual aphasic patient. In this case, activation of parts of the superior temporal lobe of the right hemisphere was exclusively associated with the use of the trained language while no such activation was observed associated with the untrained language.

3. Mechanisms of posttraumatic functional recovery

In spite of technical reservations in many individual instances, studies such as these on the posttraumatic functional recovery of linguistic abilities clearly indicate that there is a degree of "shift" of functional mediation to other structures – and presumably cases of "vicariation" (the phenomenon that brain areas with different functions can assume or "take over" the function of an injured brain region (e.g. Finger & Stein, 1982; Slavin et al., 1988)). In philosophy of mind such plastic properties of the brain have been taken as evidence for multiple realization and as an argument in favour of functionalism (e.g. Block & Fodor, 1972). As argued by Overgaard & Mogensen (2011), conclusions regarding multiple realizations require a much deeper and detailed analysis in order to utilize for instance the results of studies mapping posttraumatic task mediation. And, only by addressing more thoroughly the detailed mechanisms of posttraumatic reorganization of the brain can one achieve a thorough understanding of the degree to which functions are "relocalized" (e.g. Mogensen, 2011a, 2011c; Mogensen & Malá, 2009).

A very basic issue in this context is to address the likelihood that the basic circuitry of the brain regions lost to injury is (re)established elsewhere in the brain. This topic is discussed in detail by Mogensen (2011a, 2011c) and although even the adult brain possesses an impressive level of plasticity, it appears unlikely that the posttraumatic processes include such a recreation of lost circuitry. During maturation neurons undergo a number of changes making them less similar to those immature neurons, which originally formed the local circuitry of the brain (e.g. D.F. Chen et al., 1995; Fawcett et al., 1989; Goldberg et al., 2002). There is, however, an ongoing neurogenesis in the adult brain and this neurogenesis is potentiated by injury to the brain (e.g. Arvidsson et al., 2002; J. Chen et al., 2004; Magavi et al., 2000; Nakatomi et al., 2002; Scharff et al., 2000). Such newly formed neurons may – compared to more mature neurons – be better equipped to recreate a particular circuitry. And they may receive support in reaching the relevant brain regions since, upon injury, mature astrocytes are able to transform themselves into radial glial cells similar to those guiding the neural migration during development (Leavitt et al., 1999; Rakic, 1971, 1985). While these observations may create a level of optimism regarding the potential for recreation of lost circuitry, there is one crucial factor, which appears to prevent the adult brain (uninjured or injured) from recreating such networks. From the final stages of the original ontogenic development – and formation of the basic circuitry of the brain – a number of factors associated with glial cells and myelin appear to prevent restructuring and presumably recreation of such a basic circuitry (e.g. Berry, 1982; Schäfer et al., 2008; Schwab

& Thoenen, 1985). An especially important such factor appears to be the astrocyte-produced chondroitin sulphate proteoglycans (CSPGs). The CSPGs play an important role in termination of the developmentally "critical periods" and they are believed to "consolidate" the originally formed circuitry in its "final" form (e.g., Berardi et al., 2004; Del Rio & Soriano, 2007; McGee et al., 2005; Pizzorusso al., 2002; Schäfer et al., 2008). Apparently, the presence of these CSPGs blocks the possibility of an adult recreation of traumatically lost networks (e.g. Del Rio & Soriano, 2007; Schäfer et al., 2008). Consequently, the recreation of the basic circuitry lost to TBI or vascular incidents is unlikely to occur. Which further stresses the need for an improved understanding of the posttraumatic reorganizations and recovery-associated processes of the brain.

While clinical studies (for instance the analyses of ipsi- and contralateral contributions to posttraumatic reacquisition of language – see above) are obviously of significant importance, only well-controlled animal models (e.g. Mogensen, 2011b) can avoid some of the shortcomings of clinical studies (for instance the occurrence of subtotal lesions of brain structures as well as multiple brain regions being simultaneously affected by injury). Such animal models can also allow a degree of experimental manipulation, which is impossible to achieve in human studies. An extensive animal model-based research program (e.g. Mogensen et al., 2002, 2003, 2004a, 2005, 2007) has scrutinized the mechanisms of post-traumatic recovery processes. Utilizing a spectrum of organic and behavioural/cognitive "challenge" methods (e.g. Mogensen, 2011b; Mogensen & Malá, 2009) these studies have provided insights into the neural and cognitive processes mediating the posttraumatic functional recovery of various cognitive processes.

As reviewed by Mogensen (2011a, 2011c) and Mogensen & Malá (2009) a pattern of principles of posttraumatic functional recovery has emerged from the above-mentioned studies and others. Three general principles are especially important and describe the situation after a successful posttraumatic rehabilitation:

1. *Modification of the degree of contribution to task mediation by individual brain structures:*
   Some structures exhibit an increased or decreased level of contribution to task mediation.
2. *Task dependent and dissimilar neural substrates:*
   After a given lesion, the functional recovery of various cognitive tasks is mediated by unique and dissimilar neural substrates.
3. *Application of new cognitive strategies:*
   The fully posttraumatically recovered individuals solve the task by applying new strategies that are dissimilar to those applied pretraumatically.

Supporting the above-mentioned conclusion that posttraumatic recreation of the lost basic circuitry is unlikely, point 2 and 3 of these principles emphasize that the lost information processing (i.e. the destroyed circuitry) appear not to have returned even in case of a situation in which the individual has obtained a full functional recovery. If – within any part of the brain – the rehabilitative training had been accompanied by a recreation of a circuitry similar to that available in the pretraumatic situation, one would expect all cognitive domains affected by the lesion to posttraumatically receive equal contributions to functional recovery from the brain region within which the circuitry had been recreated. Such a situation is contradicted by Principle 2. Principle 3 contradicts the re-establishment of the information processing lost to injury. If posttraumatic processes had re-established the information processing of the injured brain structure, one would expect not only task solutions of a proficiency similar to that seen preoperatively (which is, indeed, seen in some

instances), but also that such a task solution would employ similar strategies to those of the pretraumatic situation.

3.1 The REF-model

It has to be concluded that although the brain is posttraumatically capable of a high degree of behaviourally defined functional recovery (even up to the level of a "full" recovery enabling a proficiency similar to that seen prior to injury), the brain does so without recreating the basic circuitry, which has been lost to injury. In order to account for this situation Mogensen (2011a, 2011c) and Mogensen & Malá (2009) have proposed the so-called REF (Reorganization of Elementary Functions) model. While the REF-model has primarily been developed on the basis of research focusing on posttraumatic functional recovery within the cognitive domains, it is believed to account for neural and cognitive processes, which have evolved in order to mediate behavioural and cognitive flexibility (including problem solving) in the intact brain (see Mogensen (2011a, 2011c) for further discussions).

According to the REF-model, three levels of analysis are important to the understanding of the mechanisms of posttraumatic functional recovery (see Table 1). At the lowest of these three levels are the basic information processing modules named Elementary Functions (EFs). Each EF contributes a "modular" type of information processing. The EFs are truly localized. They are at the level of true "functional localization" – in the sense that each EF is mediated by a specific substructure of a brain region. Traditionally defined brain structures (e.g. the hippocampus or the prefrontal cortex) contain the neural substrate of numerous EFs. When a brain structure is lost to injury, all EFs mediated by the subregions within that structure are irreversibly lost. Presently, the functional properties of the individual EFs are poorly characterized. The conceptual distance between the EFs and what is traditionally defined as cognitive or "psychological" functions is significant. When characterization of an EF becomes possible, it is likely that the functional properties of EFs may best be described in mathematical terms rather than in the vocabulary of cognitive psychology. At the top of these three levels are the surface phenomena of behavioural and/or mental manifestations – including cognitive awareness. It is at the level of these surface phenomena that the symptoms upon brain injury are normally characterized (in terms of behavioural and/or cognitive impairments) and it is also at the level of the surface phenomena that post-traumatic functional recovery is normally observed – be it in clinics or in most cases of animal model-based experiments. To bridge the gab between the non-recovering EFs and these surface phenomena, the level of Algorithmic Strategies (ASs) has been inserted.

Each AS consists of numerous interacting EFs. ASs are primarily established as a consequence of experience and learning – although some may be genetically preprogramed. The neural substrate of an AS consists of the neural substrates of all its constituent EFs plus the interconnections between the neural substrates of these EFs. Therefore, while an EF is strictly localized to a particular subregion of a brain structure, most ASs are distributed across many regions of the brain. The information processing of an AS is the mechanism mediating a specific surface phenomenon (e.g. a specific solution of a specific task). Most surface phenomena can be realized via the activity of a multitude of ASs. The task solutions achieved via activation of various ASs may provide outcomes of similar proficiency and unless special analytical techniques are employed, it is at the surface level not possible to discriminate between behavioural phenomena reflecting two related but different ASs. When injury destroys the neural substrate of one or more of the constituent EFs within an

AS, that AS (and as a consequence the surface phenomenon relying on that AS) is lost and posttraumatically this surface phenomenon is impaired.

SURFACE PHENOMENA (Mental/Behavioural manifestation level) • Final products in terms of mental states (potentially conscious) and overt behaviour • Realized by a multitude of individual Algorithmic Strategies (ASs)
ALGORITHMIC STRATEGIES (ASs) • Consists of numerous interacting Elementary Functions (EFs) • Mostly a result of experience and learning *Neural substrate:* The substrate of the constituent EFs plus the interconnections between these EFs – that is: most ASs are distributed across many regions of the brain
ELEMENTARY FUNCTIONS (EFs) • Truly localized • Perform basic information-processing *Neural substrate:* Substructures/local circuits – within a given brain structure – that is: EFs are fully localized

Table 1. The three levels of analysis of the REF-model – including some of the characteristics of Algorithmic Strategies (ASs) and Elementary Functions (EFs). For further details, see the present text as well as Figs. 1 and 2 in Mogensen & Malá (2009) and Fig. 1 in Mogensen (2011a).

An individual may encounter the demand for a task solution for which there is no established procedure available in at least two different contexts. The situation (and task) may be of a novel nature, thereby presenting the intact individual with a previously unexperienced situation (to which there is no obvious generalization from previous experience). Or the situation may in reality be known from previous experience, but brain injury has robbed the individual of the possibility of utilizing previously established procedures. Whether for one or the other of these reasons – in the terminology of the REF-model – the situation is not a priori associated with activation of a specific AS. In such situations, a process of activation of individual ASs as mediators of behaviour is initiated (see Fig. 1). The quality of the resultant behaviour and/or conscious representation is evaluated and in case of success a future association between that situation and the tested AS is established. In case of failure, an alternative AS is activated and evaluated – thereby continuing a process potentially including the evaluation of numerous pre-existing ASs (for further descriptions see Mogensen (2011a, 2011c) and Mogensen & Malá (2009)). This process bears some resemblance to what was described as the "hypothesis" evaluation of Krechevsky (1932, 1933). The selector/evaluator mechanism controlling the activation and evaluation of ASs resembles (but is not identical to) the "Supervisory Attentional System" (SAS) of Norman & Shallice (1986). If a pre-existing AS is eventually found to successfully give rise to the required surface phenomenon, the situation will in the future be associated with activation of that AS. The neural plasticity involved in this process consists of modified connections within the selector/evaluator mechanism. This plasticity mediates the future association between the situation in question and the selection and activation of successfully utilized AS.

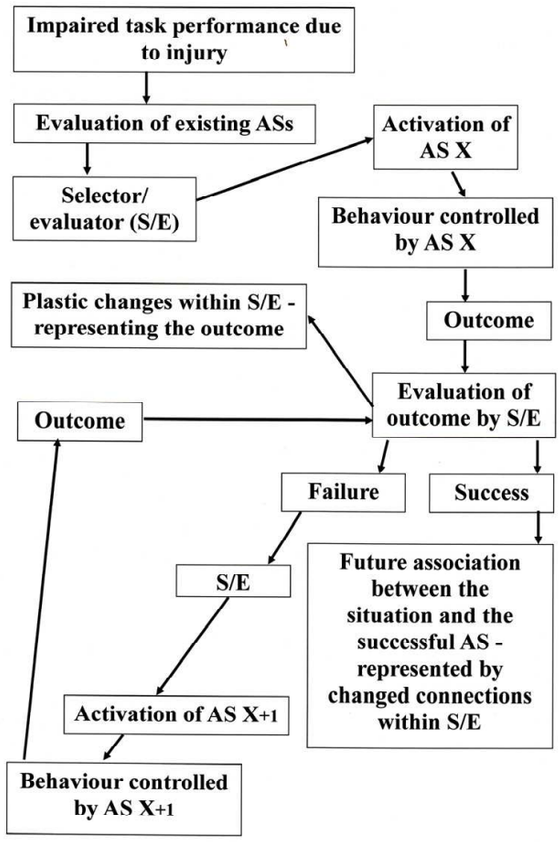

Fig. 1. Flow diagram depicting the sequence of events which according to the REF-model leads to a successful functional recovery after brain injury – provided that a pre-existing AS can achieve a successful task solution. For further details see the present text as well as Figs. 3, 4, and 5 in Mogensen & Malá (2009), Fig. 1 in Mogensen (2011c), and Fig. 2 in Mogensen (2011a).

If the evaluation of existing ASs does not lead to a successful task solution, a novel AS will have to be created and associated with the situation in question. The creation of a novel AS involves a reorganization of the functional interactions between EFs and is the actual "Reorganization of Elementary Functions" (REF) process. This reorganization (see Mogensen, 2011a, 2011c; Mogensen & Malá, 2009) includes a type of process resembling the backpropagation algorithm (e.g. Rumelhart & McClelland, 1986; Werbos, 1994). A schematic and simplified representation of this process is illustrated in Fig. 2 (and in Fig. 5 in Mogensen & Malá, 2009). Utilizing such a backpropagation-resembling process, a set of EFs – which previously did not constitute an interacting entity – is functionally united to form a novel AS. Most likely, backpropagation mechanisms constantly modify the connectivity between EFs. The outcome of an attempted task solution (whether successful or not) results (in parallel to the feedback to the selector/evaluator mechanism regarding the degree of success of the attempted task solution) also in a backpropagation process modifying the connectivity (and consequently functional interaction) between individual EFs. This is illustrated in Panel B of Fig. 2 while Panel A and C, respectively, illustrates the (highly simplified) functional interactions (and connectivity between neural substrates) of

individual EFs. While many of the interconnections between EFs remain unchanged between Panel A and C, a number of changes have occurred. The most striking may be that EF 22 and EF 47 – which originally (Panel A) did not participate in AS X and AS X+1, respectively – are now integrated into the network of these two ASs. Furthermore, EF 53 – which originally (Panel A) was part of AS X+2 – no longer (Panel C) participates in the information processing of AS X+2. Examples of other changes are a strengthening of the connectivity and functional interaction between EF 2 and EF 16 as well as a weakening of the connectivity and functional interaction between EF 39 and EF 16. As is illustrated in Panel D of Fig. 2, the backpropagation mediated plastic changes – and thereby reorganization of functional relationships between EFs – can result in the creation of a network, which in itself constitutes the basis for a novel AS – in this case AS X+3.

It is important to notice that what is modified as a result of this backpropagation-mechanism is the connectivity between EFs rather than any aspect of the internal circuitry of the EFs. According to the REF-model, the circuitry of individual EFs as well as their information processing remains unchanged by these processes. They do, however, perform that information processing in a novel context and on information of novel sources. Within the domains of sensory and perceptual analysis examples of a somewhat related process can be found. In individuals in whom one of the hands has been amputated, the region of somatosensory cortex, which used to represent the now missing hand, does not remain "vacant". Instead, the neighbouring somatosensory regions (representing the arm and face, respectively) encroaches on the "vacant" area in such a way that the original hand area is eventually fully taken over by inputs from arm and face, respectively (e.g. Karl et al., 2001; Weiss et al., 2000; Yang et al., 1994). Also, training restricted to part of the body may be associated with relative shifts within the somatosensory representations (e.g. Elbert et al., 1995; Merzenich & Jenkins, 1993; Münte et al., 2002; Xerri et al., 1996). Somewhat similar processes are found within the auditory system where the tonotopic representations at various levels may be reorganized as a result of both partial loss of input (e.g. due to restricted cochlear lesions) and learning experiences in intact individuals (e.g. Irvine, 2007; Recanzone et al., 1993; D. Robertson & Irvine, 1989; Scheich, 1991; Thai-Van et al., 2007). In all of these instances neural "modules", which originally performed their information processing (and contribution to sensory and perceptual processes) on information from one part of the body or aspect of the tonotopic spectrum, respectively, received a modified input but most likely continued to perform identical or rather similar information processing on information from another part of the body or tonotopic spectrum, respectively (for further discussion: see Mogensen, 2011a, 2011c; Overgaard & Mogensen, 2011). At least some cases of intermodal plasticity (e.g. Bach-y-Rita et al., 1969, 1998; Kaczmarek et al., 1991; Ptito et al., 2005) may provide somewhat related examples. For instance, in "early blind" individuals Ptito et al. (2005) found a spatial orientation discrimination performed on somatosensory information to be partly mediated by a cortical region, that in sighted individuals is associated with the performance of visual tasks in which the spatial orientation of figures are to be determined. As discussed further by Mogensen (2011a, 2011c), the cortical region in question may have contributed the same type of information processing in sighted and blind individuals, respectively, but receiving the relevant inputs from visual and somatosensory inputs, respectively.

As mentioned above, the processes described by the REF-model are likely to have evolved in the context of problem solving, and behavioural as well as conscious flexibility in the intact individual (Mogensen, 2011a, 2011c). They, however, automatically also become the

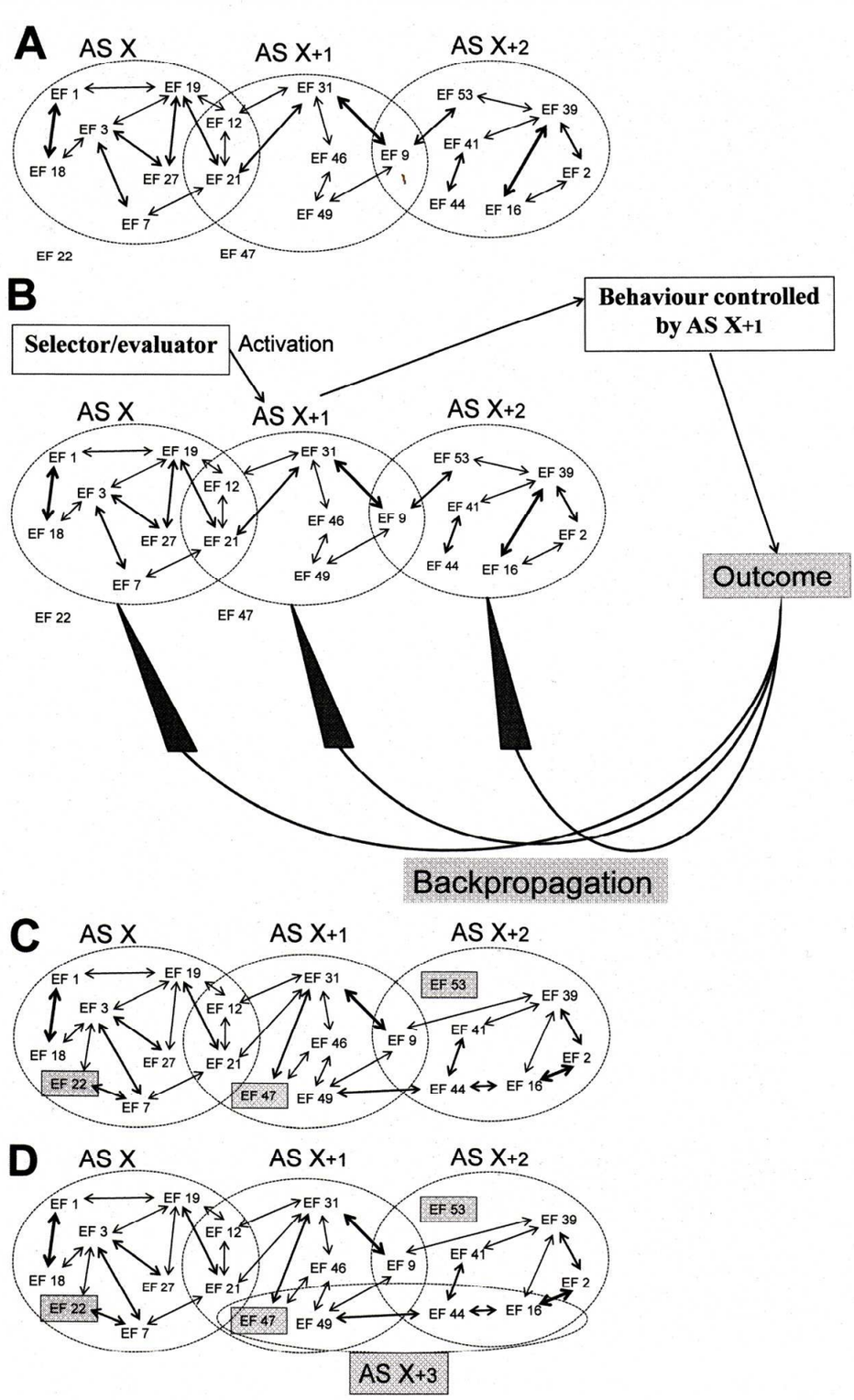

Fig. 2. Schematic and simplified representation of the experience-associated reorganizations of connectivity between the neural substrates of EFs (for further discussion: see the text).

mechanisms of posttraumatic functional recovery when brain injury robs the individual of the EFs, ASs, and thereby mechanisms, which pretraumatically allowed a particular task to be solved. What was pretraumatically associated with an efficient task solution (activation of an appropriate AS in the terminology of the REF-model) is posttraumatically equivalent to a "novel problem solving situation" and thereby calls for the above-described mechanisms of search for an adequate AS and potentially the creation of a novel AS.
Posttraumatically, the behaviourally defined "complete functional recovery" is in the context of the REF-model to be seen as a situation in which the posttraumatic task solution is accomplished via an AS, that allows behavioural manifestation which cannot – but for a detailed (and most often not performed) behavioural/cognitive analysis – be distinguished from the behaviour occurring pretraumatically. The apparent contradiction between "functional localization" and "functional recovery" is, according to the REF-model, the result of a "confusion of levels" regarding the term "function". The term "function" is used in two different contexts. What is truly localized is the information processing of the individual EFs – an information processing which is permanently lost when the neural substrate of those EFs are destroyed by injury. On the other hand, the "functional recovery" is observed and defined according to the surface phenomena, which can posttraumatically be achieved at a more or less similar proficiency to that seen pretraumatically via the activation of alternative ASs (which do not depend on the EFs lost to injury) (for further discussion: see Mogensen, 2011a, 2011c; Mogensen & Malá, 2009).

4. Implications of the REF-model for posttraumatic rehabilitative training

One of the implications of the REF-model is that the neuroplastic changes, which are essential to the mediation of posttraumatic cognitive recovery, are "instructed" by two types of feedback regarding the outcome of the processes in which the behavioural manifestations of a particular AS meet the current environment: the feedback to the selector/evaluator mechanism (e.g. Fig. 1) and the backpropagation mechanism instructing the reorganization of the connectivity between EFs (Fig. 2) (see further discussions in Mogensen, 2011a, 2011c; Mogensen & Malá, 2009). As stressed by Mogensen (2011a) it can be argued, that it is at the level of the surface phenomena that the primary causation of plastic changes is to be found. When the functional manifestations at the surface level interact with a specific environment, the feedback and backpropagation mechanisms lead to a "downward causation" according to which AS-selection and potentially creation of a novel AS is achieved. This is a situation with important implications for clinical practise in terms of rehabilitative training.
The outcome of the specific interaction between the individual and the current environment is the source of both the plastic modifications within the selector/evaluator mechanism and the modified connectivity between individual EFs. Consequently, the future nature as well as selection of ASs related to a particular task depends crucially on the situation in which the training leading to posttraumatic functional recovery has occurred. One may, in other words, expect a potentially worrying degree of situational dependence of the outcome of the rehabilitative training. As discussed elsewhere (e.g. Mogensen, 2011a, 2011c; Mogensen & Malá, 2009; Wilms & Mogensen, 2011) a rehabilitative training program may lead to highly proficient task solutions in the particular task and training setting administered in the clinical context – while unfortunately having little or no generalization to the everyday life situation of the patient. Therefore, patients might appear fully "recovered" when subjected to formal testing in a hospital or other clinical setting while subsequently demonstrating

severe recidual problems in non-institutionalized contexts (e.g. Mogensen, 2011a; Wilms & Mogensen, 2011).

An important implication of this situation is that as far as possible rehabilitative training should be conducted under circumstances optimizing generalization to the everyday environment of the patient. Ideally, training within clinical institutions should be organized in manners resembling the everyday challenges of the patient's home and potentially workplace. Furthermore, training should be continued as seemlessly as possible into the daily environment to which the patient eventually returns after leaving the hospital and/or other institutions. Utilization of advanced technology is a growing and important field within neurorehabilitation. The use of such technologies may contribute towards realizing the ideal of "life-like" training situations in the institution and the possibility of continuing rehabilitative training in an "out-of-institution" setting. The development of virtual reality settings and utilization of these in rehabilitative training holds the promise of much more life-like training situations in the institution. Utilization of various hand-held micro-computers and similar devises may allow a relatively formalized but highly flexible "training" to continue into the daily life of the patient. An example of the latter may be the success of the "NeuroPage" project (e.g. Wilson et al., 1997) in which hand-held devises support and ease the daily life of amnestic patients – while also producing apparent training effects, which makes the NeuroPage not only a "cognitive prosthesis" but makes it part of an actual rehabilitative training process (e.g. Wilson et al., 2001).

The utilization of computers and other types of advanced technology in the rehabilitative training of brain injured patients obviously holds significant promise – not the least regarding possibilities of creating a more "ecologically valid" cognitive training by "bringing reality into the institution" (e.g. via utilization of virtual reality settings) and "bringing training into the real world" (e.g. by utilizing devices like the above-mentioned NeuroPage and even more advanced hand-held devices) (for further discussions, see for instance Wilms & Mogensen, 2011). In parallel to the important potentials to provide a more "ecologically valid" training situation, the use of advanced technologies also promise a number of other already realized and not the least potential benefits. Rehabilitative training may, for instance, become more intensive by supplementing the (time and financially highly demanding) face-to-face therapeutic sessions with a therapist with training sessions in which the patient exclusively interacts with technological devises (e.g. Katz, 2009; Rizzo et al., 2004; Tsirlin et al., 2009). Also, utilization of computer systems based on artificial intelligence (e.g. Wilms, 2011) can allow advanced technology-based training systems to adapt in highly flexible and dynamic manners to many aspects of the progress of the patient. The pattern of progressions in task performance during cognitive recovery after brain injury is often highly dissimilar between patients and therefore requires a dynamic and adjustable approach in order to provide the optimal training parameters (e.g. I.H. Robertson & Murre, 1999). Another way in which the effects of training may be measured and utilized in the guidance of the progression of training is by inclusion of the novel – but promising – area of brain-computer interactions (e.g., Coyle et al., 2003). Such techniques may allow the training situation – including the demands and feedback to the patient – to be steered by direct measurements of neural activity (e.g. Coyle et al., 2003; Daly & Wolpaw, 2008; Sitaram et al., 2009). Obviously, in order to obtain the optimal utilization of such brain-computer interactions, one needs a thorough (and presently only partly existing) knowledge of the neural processes mediating the desired functional rehabilitative process.

When utilizing advanced technologies in the context of cognitive neurorehabilitation one needs, however, to exert a high degree of caution (as well as extensive subsequent testing of methods) when translating more traditional types of training to for instance a computer-based setting. As is stressed by Wilm & Mogensen (2011), naïve "translations" from for example a "paper and pencil" version of a test or training procedure to a computer-based version may create unexpected discrepances between the two versions. While this situation poses a significant challenge to the clinical utilization of advanced technologies, it also provides a "window" through which cognitive neuroscience may gain an improved understanding of some of the cognitive mechanisms mediated by the intact and injured brain. Such an example can be seen in the results of Wilms & Malá (2010). In patients suffering hemispatial neglect (e.g. Rossetti et al., 1998) the so-called Prism Adaptation Therapy (PAT) (e.g. Frassinetti et al., 2002; Rossetti et al., 1998) may be used successfully. In PAT, the patients are trained in a task requiring them to point (without being able to follow their arm visually during the pointing movement) to targets defined by the therapist. While doing so, the patient is wearing prism goggles, which diverts the visual field ten degrees to the right (the patients are exhibiting a hemispatiel neglect of the left hemispace). In the traditional version of PAT, the feedback provided to the patient is the sight of the pointing finger at the moment when the pointing movement has been terminated. In most cases, the patient gradually adapts to the perceptual shift and eventually shows an after-effect in the form of a relative shift of the pointing movement. This shift even persists after the removal of the goggles. In other words, the procedure constitutes an at least partial therapeutic intervention regarding the neglect of the left hemispace. An essential element of the procedure is the feedback regarding the precision of the pointing movements during the training period (e.g. Frassinetti et al., 2002; Sarri et al., 2008; Serino et al., 2006, 2007). Wilms & Malá (2010) included in their study this traditional version of the PAT-procedure and compared it directly to a procedure in which the patients pointed to a touch-sensitive computer screen and feedback was provided graphically (in the form of an X) on the screen rather than via the direct sight of the pointing finger. Surprisingly, in both patients and uninjured subjects the outcome from the two procedures differed significantly – the version in which an icon on the computer screen provided the feedback resulted in significantly less after-effects than the traditional version. While being unexpected, these results emphasize – as is stressed by the REF-model – that the exact setting of the training procedure as well as the nature of the feedback provided to the patient are crucial factors for the outcome of neurorehabilitative training (e.g. Wilms & Mogensen, 2011). Furthermore, the results are potentially reflecting some of the same processes as those emphasized by a model published by Milner & Goodale (1995, 2008) – a model stressing the likelihood that visual feedback may be processed along different channels depending on the circumstances of its presentation.

Amongst the important factors shaping the outcome of rehabilitative cognitive training after brain injury are not only the therapeutic setting (e.g. institutionalised/daily life environment) and the details of the type of feedback provided to the patient. Equally important components spring from the pretraumatic experience and cognitive profile of the patient. As is obvious from the REF-model, the spectrum of ASs available during posttraumatic functional recovery is crucial to the efficacy of training. This effect is not limited to cases where activation of a pre-existing AS may achieve successful task solution (as indicated in Fig. 1). Even if no spared AS, in itself, is able to mediate a successful task solution, the interconnectivity between the neural substrates of EFs – viewed at the cognitive level: the

pre-existing interactions between individual EFs – are crucial "building blocks" in the process of shaping new and successful ASs (as shown in Fig. 2). On such a basis one can expect the speed, efficacy and for that matter eventual outcome of rehabilitative training to be highly dependent on the pretraumatic cognitive status of the patient. If the brain injured individual posttraumatically still possesses varied and proficient ASs within a number of cognitive domains related to the area in which the symptoms are seen, one will – all other factors equal – expect a more proficient and potentially quicker recovery process.

But not only the efficacy of rehabilitative training but also the cognitive nature of the outcome achieved via such training may depend crucially upon pretraumatic cognitive factors (i.e. the nature of available ASs). An example of this may be seen in a series of fascinating observations regarding training-induced increases in utilization as well as subjective awareness of originally not consciously perceived stimuli in the metacontrast masking experimental setup (e.g. Schwiedrzik et al., 2009). The context of these experiments is that both clinical and experimental data point to the fact that brain injured individuals exhibiting "blindsight" can improve their task performance with training. For instance, improved performance in a forced choice procedure can be seen in both monkeys suffering bilateral ablation of the primary visual cortex (V1) (Dineen & Keating, 1981; Humphrey, 1974) and in patients demonstrating blindsight (e.g. Bridgeman & Staggs, 1982; Chokron et al., 2008; Henriksson et al., 2007; Raninen et al., 2007; Stoerig, 2006; Zihl, 1980; Zihl & Werth, 1984). Often, such improvements are not accompanied by any change in subjective awareness of the stimulus – in general, patients exhibit blindsight by behavioural demonstrations of a "perceptual processing" of the stimulus without showing any conscious awareness of the stimulus. However, there is now a growing body of evidence demonstrating that perceptual training can also increase the reported perceptual awareness of stimuli in blindsight patients (e.g. Sahraie et al., 2006). Also, studies in intact subjects exposed to subliminal presentation of visual stimuli (mostly utilizing the above-mentioned metacontrast masking in a "stimulus onset asynchrony" paradigm) have demonstrated that even in individuals without injury to the brain, training can increase the degree of perceptual awareness of a stimulus originally unavailable to consciousness (e.g. Albrecht et al., 2010; Schwiedrzik et al., 2009). In the context of such metacontrast masking experiments (e.g. Schwiedrzik et al., 2009) it appears that individual differences between normal subjects reflect dissimilar solution strategies (i.e. selection of dissimilar ASs) (Albrecht et al., 2010). When individuals displaying such dissimilarities at the outset of training are subjected to identical training procedures, it turns out that the solution strategies become even more dissimilar during the period of training – demonstrating a potentiation rather than an elimination of these strategy differences (Albrecht et al., 2010). Results such as these emphasize that subjecting individuals with pre-existing differences in the available ASs as well as the potential differences in "biases" of the selector/evaluator mechanisms to identical rehabilitative training may not necessarily shape the cognitive processes in question in one particular direction. Rather, it may produce different outcomes depending on the pretraumatic condition of the patients.

Especially in the context of Alzheimer's dementia – but also with references to traumatic and vascular acquired brain injury – a somewhat related discussion deals with the issues of "brain reserve" (e.g. Scheibel et al., 2009) and "cognitive reserve" (e.g. Fuentes et al., 2010; Kesler et al., 2010; Ropacki & Elias, 2003; Stern, 2002). Both of these concepts refer to situations in which the pretraumatic condition influences the degree to which patients posttraumatically (or, for instance, during degenerative neural processes such as those seen

in Alzheimer's dementia) are able to "compensate" for the neural and cognitive loss sustained due to injury and/or degeneration. While "brain reserve" primarily emphasizes structural aspects of the brain (e.g. density of synaptic contacts), the emphasis in "cognitive reserve" is on the availability of cognitive processes and strategies. In the context of the REF-model, "brain reserve" should be seen as an analysis of the degree of connectivity between the neural substrates of individual EFs, while "cognitive reserve" in general refers to more or less the same – but analysed at the cognitive level of the ASs. There may in "brain reserve" be a tendency to (over-)stress the quantitative aspects of synaptic connectivity, while according to both the idea of "cognitive reserve" and the REF-model it must be emphasized that what may be most important to the posttraumatic performance and potential of the patient is rather the quality (shape) of the patterns of synaptic connections (as opposed to the potentially less informative raw count of synaptic connections). A somewhat related phenomenon may be found within the research area dealing with the potentially "cognitively enhancing" effects of an upbringing in an "enriched" (varied and stimulating) environment (e.g. Rosenzweig, 1971). Much of the initial research within this area (e.g. Bennett et al., 1964, 1969; Renner & Rosenzweig, 1987; Rosenzweig et al., 1961) primarily focused on biochemical and anatomical effects on the brain – directly or indirectly assuming such changes to manifest themselves in cognitively "enhancing" consequences. It has, however, turned out that such environments may not always be "cognitively enhancing" in a more global sense. Rather, the consequences may be a changed tendency to select particular solution strategies (ASs in the terminology of the REF-model) (e.g. Mogensen, 1991). In other words: to fully understand the potential consequences of the prehistory of an experimental animal or a patient, one needs to address not only the quantitative but also the qualitative aspects of modified connectivity of the brain.

5. Supporting the posttraumatic rehabilitative process

As described above, according to the REF-model some of the essential aspects of the mechanisms mediating posttraumatic cognitive rehabilitation are the reorganization (and to an extent recruitment) of preserved networks more or less distal from the site of trauma as well as plastic modifications of the neural connectivity between such networks. Consequently, it is likely that the posttraumatic rehabilitative processes can be supported by interventions which are able to (1) promote the optimal survival of originally undamaged networks (i.e. the integrity of originally unaffected EFs), and (2) create the optimal conditions for plastic reorganizations of the connectivity between such networks.

A prerequisite for the optimal functioning – including plastic abilities – and ultimately the survival of neurons is an adequate supply of neurotrophic factors (including the neurotrophin Brain Derived Neurotrophic Factor (BDNF)) (e.g. Kafitz et al., 1999; Levi-Moltalcini, 1982, Lewin & Barde, 1996). BDNF is produced by glial cells as well as neurons and the supply to a neuron – in the form of synaptic take-up followed by retrograde axonal transport – is mostly achieved as part of the synaptic interaction within an efficient functional network (e.g. Hamburger, 1934, 1975; Hollyday & Hamburger, 1976; Levi-Montalcini, 1982; Levi-Montalcini & Levi, 1942). When the brain is injured, the primary injury (mechanical impact or immediate and local consequences of a vascular incident) is followed by further degeneration within more distal parts of the brain – known as secondary and tertiary degeneration. One of the many (e.g. B.K. Siesjo & P. Siesjo, 1996) mechanisms of this secondary and tertiary degeneration is that neurons within these parts of

the brain have lost the possibility to interact (and receive for instance BDNF as part of that interaction) with neurons lost to the primary injury (e.g. Sofroniew et al., 1993). Therefore, it may be assumed that interventions which can boost the production (transcription) – and thereby availability – of BDNF (as well as other neurotrophic factors) may have the potential to support the posttraumatic rehabilitative process by both preserving as much as possible of the originally uninjured parts of the brain and by optimizing the neuroplastic potentials of these preserved brain regions.

The hormone erythropoietin (EPO) has long been recognized as crucial to the production of erythrocytes (and utilized clinically in this capacity). More recently, however, it has been demonstrated that there is a separate production of EPO and EPO-receptors in the brain (e.g. Baciu et al., 2000; Hasselblatt et al., 2006; Silva et al., 2006). In the central nervous system, EPO has a broad range of effects (e.g. Mammis et al., 2009) – including stimulation of the production of BDNF (e.g. Viviani et al., 2005; F. Zhang et al., 2006). EPO significantly increases BDNF-production when administered 6 or 24 hours after a traumatic brain injury (Mahmood et al., 2007).

By now, numerous techniques have demonstrated the neuroprotective abilities of EPO (e.g. Grasso et al., 2007; Mammis et al., 2009; Y. Zhang et al., 2009). The close association between EPO and blood-related processes originally provoked a primary research focus around the use of EPO in vascular brain injury (e.g. Alafaci et al., 2000; Brines et al., 2000; Buemi et al., 2000; Calapai et al., 2000; Grasso, 2001; Siren et al., 2001; Springborg et al., 2002). Subsequently, however, it turned out that EPO possesses a strong therapeutic potential even in TBI – including the ability to reduce posttraumatic cognitive impairments and support the cognitive rehabilitative processes (e.g. Lu et al., 2005; Malá et al., 2005, 2007; Mogensen et al., 2004b, 2008a, 2008b; Wang et al., 2006). The degree to which such therapeutic effects are mediated via stimulation of BDNF remains unknown, but it is obvious that further research is needed in order to clarify some of the intricacies of the therapeutic use of EPO. For instance, it appears that EPO administered at the moment of TBI may have a more pronounced ability to support posttraumatic cognitive recovery, if the rehabilitative training is initiated relatively soon after injury as opposed to later (Malá et al., 2005, 2007). Also, the relationship between EPO and BDNF is not restricted to the EPO-provoked stimulation of BDNF-production (e.g. Viviani et al., 2005; F. Zhang et al., 2006) – another aspect of the relationship is that BDNF induces EPO-expression – demonstrated at the levels of both the mRNA and protein (Wu et al., 2010).

The production of BDNF may also be enhanced by physical activity in the form of exercise (e.g. Griesbach et al., 2004a, 2004b, 2009; Moltini et al., 2004; Vaynman et al., 2003; M. Gajhede, E. Wogensen, G. Wörtwein & J. Mogensen, in preparation). And although much needs to be explored within this area, a growing number of publications from recent years (e.g. Arida et al., 2009; Devine & Zafonte, 2009; Griesbach et al., 2004a, 2004b, 2009; Hayes et al., 2008; Luo et al., 2007; Malá et al., 2008; Seo et al., 2010) have demonstrated that various types of physical activation and exercise are able to promote the posttraumatic functional recovery and rehabilitation after various types of brain injury. At least in certain instances, it has been shown that the exercise-induced improvements of cognitive abilities after brain injury depend upon stimulation of the production of BDNF (Griesbach et al., 2009). In animal models, exercise and other types of physical activation are studied under conditions of both "voluntary" and "forced" exercise – where the "forced" variants typically are associated with at least a certain level of stress and consequently increased production of the "stress-hormone" corticosterone

(CORT). Increased serum concentrations of CORT has been found to reduce the production of BDNF (e.g.. Adlard & Cotman, 2004; Duman et al., 1997). On this background, it is not surprising that Luo et al. (2007) have demonstrated that while voluntary exercise acts therapeutically in brain injured individuals, the stressful and forced variant has no such effects. But even in this context, a highly promising avenue in the support of posttraumatic rehabilitation after brain injury is in clear need of additional research. In contrast to the results of Luo et al. (2007), Hayes et al. (2008) and Malá et al. (2008) have independently documented significant therapeutic effects of forced and stress-associated types of physical activation. Furthermore, the stress-associated method originally published by Malá et al. (2008) has been found to be associated with both an increase in the serum concentration of CORT and (surprisingly) an increased concentration of BDNF in the hippocampus and the prefrontal cortex (M. Gajhede, E. Wogensen, G. Wörtwein & J. Mogensen, in preparation). Clearly, the optimal utilization of several of these highly promising ways of supporting the posttraumatic rehabilitative processes can only be fully utilized (not to mention understood) in the light of future research.

6. Conclusion

The neuroplasticity mediated cognitive rehabilitative processes upon brain injury are frequently divided into two phases: initially a relearling of compromized and/or lost "functions" followed by later compensational processes which support the behavioural abilities without re-establishing what has been lost to injury (e.g. Stein & Hoffman, 2003). According to the REF-model, such a distinction is likely to be somewhat artificial and potentially misleading regarding the possibility of major re-establishment of lost functions – at least if "function" is considered at the level of the EFs. As mentioned above and discussed extensively elsewhere (Mogensen, 2011a), re-establishment of the lost neural substrate of EFs is unlikely to occur. However, as noted by Mogensen & Malá (2009), subtotal lesions of various structures (or more likely substructures) of the brain may allow a degree of "re-establishment" of the original substrate of task mediation via mechanisms such as those suggested by I.H. Robertson & Murre (1999). If such a process leads to re-establishment of the substrate of EFs originally lost to trauma, an actual "relearning" may indeed take place. But in general, a distinction between "relearning" and "compensation" will (according to the REF-model) in most if not all cases reflect the degree to which the surface level phenomena can easily be distinguished from those seen pretraumatically – while both "relearning" and "compensation" in reality reflect the REF-processes.

At the theoretical level, the REF-model has provided a framework within which the concepts of localization of function and functional recovery can co-exist. But it has also provided a structure within which connectionist networks (e.g. McClelland et al., 1986; McLeod et al., 1998; Rumelhart & McClelland, 1986) can co-exist with "modularity" (e.g. Fodor, 2000; Pinker, 1999). The functionally very specialized EFs place the REF-model within the framework of what is called "Massive Modularity" (e.g. Barrett & Kurzban, 2006) and it consequently embraces the idea of "rules of computation" associated with such modularity-based models. Since, however, at the level of the ASs the REF-model must be considered connectionist and distributed – and the ASs are established and modified according to backpropagation mechanisms – the basis for an AS is more or less a

connectionist network of interconnected EFs. Via this combination, the REF-model can accommodate both the modularity-based predictability of for instance lesion effects and the connectionist flexibility and potential for dynamic reorganizations, which allow behavioural and cognitive flexibility in the intact individual as well as the posttraumatic cognitive rehabilitation of the brain injured patient.

As stressed above, the way the REF-model conceptualizes the mechanisms of posttraumatic cognitive recovery points to a number of important issues to consider clinically:

It is important to provide supportive therapeutic interventions which can limit secundary and tertiary neurodegeneration as well as create the optimal conditions for the plasticity required for the reorganization of connectivity between the neural substrates of EFs (as well as within the selector/evaluator mechanisms). As mentioned, this may be done utilizing pharmacological interventions and/or exercise. And there is little doubt that future research will provide additional ways of accomplishing this – potentially by combining for instance environmental enrichment and various types of training (e.g. Hicks et al., 2007).

And perhaps the most important aspect in at least a short term clinical perspective is the ways in which the REF-model puts focus on the fact that rehabilitative training is situationally dependent – and not the least the dependence on the specific types of feedback provided during training. In order to achieve a cognitive rehabilitative training that can generalize to the everyday situation of the patient – and thereby provide the types of ecologically valid "recovery" which remains the goal of all such efforts – significant efforts and progress must be invested in optimizing training methods. Including the creation of training which can bridge the therapeutic situation in an institution and the subsequent life of the recovering brain injured patient.

In order to achieve all of these goals, progress within technology, medical practise as well as research at the conceptual and empirical levels is required. And an adequate synthesis between the results from all of these (and many other) areas must be achieved. The REF-model is a theoretical framework within which some of these steps may be achieved. However, in its present form it is but a first sketch. Further improvements and refinements of the REF-model as well as our understanding of cognitive rehabilitation after brain injury will grow from the continued research as well as the daily marriage between clinical and research efforts.

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8. References

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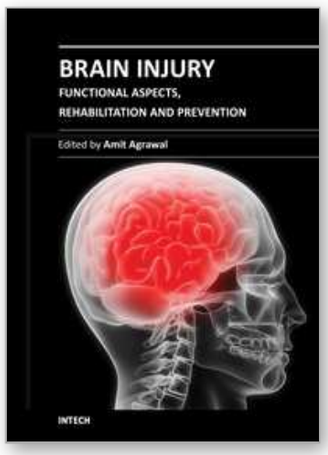

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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