4 Discussion

4.1 Summary

The aim of the present thesis was to investigate the behavioral and neural effects of stimulating the noradrenergic system in healthy subjects and stroke patients with motor deficits.

At the behavioral level, healthy subjects were tested with several tasks of varying motor complexity and sensorimotor demands. The data showed that stimulating healthy subjects with a single dose of selective noradrenaline reuptake inhibitor reboxetine (RBX) had a differential effect on visuomotor performance: while simple repetitive motor paradigms such as index finger tapping and rapid pointing movements were unaffected by RBX, tasks relying on visuomotor coordination and hand-object interactions in 2D and 3D space showed significant improvements in motor performance (Figure 3.1.1) when subjects had received RBX (compared with PBO). Importantly, increased movement speed in these tasks was not at the cost of movement accuracy as error rates or pathway length did not differ between RBX and PBO condition. The observed effects were not correlated with the individual RBX plasma levels.

At the neural level, fMRI was used to investigate RBX-mediated neural mechanisms underlying visuomotor processing during goal directed hand movements as probed by a joystick task. The improvements in visuomotor performance were associated with enhanced activity in right hemispheric areas known to be involved in visuospatial attention and motor control (Figure 3.1.3). The connectivity analysis showed that these differential activations can be explained by increased coupling of right V1, IPS, and FEF/dPMC with left hemispheric areas, which was independent from task difficulty (Figure 3.1.5). Hence, stimulating the NA system with RBX mediated a bihemispheric
rearrangement of the functional network architecture that might have enabled a more efficient implementation of the visuospatial capacities of the right hemisphere, thereby improving behavioral performance in the joystick task.

In stroke patients, the results showed that stimulation with RBX significantly increased maximum grip power and index finger tapping frequency of the paretic hand. RBX-mediated improvements in tapping performance at the paretic hand were associated with a reduction of pathological overactivity in both hemispheres, including ipsilesional ventral premotor cortex (vPMC), supplementary motor area (SMA), and temporoparietal junction (TPJ), as well as bilateral dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Figure 3.2.2, Figure 3.2.3 & Figure 3.2.4). The connectivity analyses revealed that this reduction of overactivity was accompanied by a normalization of ipsilesional SMA-M1 connectivity towards physiological levels during movements of the affected hand (Figure 3.2.6). The data suggest that the behavioral deficits of stroke patients might be ameliorated by enhancing interregional coupling of key motor areas via noradrenergic mechanisms, thereby correcting pathological network interactions underlying motor disabilities.

4.2 Detailed discussion

4.2.1 Pharmacological modulation of behavior

*Improving behavior in humans by pharmacological stimulation*

There has been a long discussion about whether or not cognitive performance can be improved under physiological conditions by means of pharmacological or technical (e.g., TMS) interventions. There is, however, a growing body of evidence that for different tasks even a single application of a centrally acting drug can significantly improve behavioral performance. For example, performance was demonstrated to be enhanced over and above placebo in a language learning task by stimulating adrenergic receptors
(Breitenstein et al., 2004), in a visuospatial attention task by stimulating nicotinic receptors (Vossel et al., 2008), and in a working memory task by stimulating dopaminergic receptors (Mueller et al., 1998).

A crucial role of monoaminergic neurotransmission (i.e., noradrenaline, dopamine and serotonin) on motor functions has been suggested by several studies with both healthy subjects and patients. For example, in Parkinson’s disease, the lack of dopaminergic stimulation of the basal ganglia is seen as the primary cause for bradykinesia and muscle rigidity, which can be relieved by administration of the dopamine precursor levodopa (Cotzias et al., 1969). The same drug has also been shown to significantly support recovery of function in patients suffering from hemiparesis due to stroke when levodopa administration was paired with physiotherapy (Scheidtmann et al., 2001). However, animal studies showed that these effects might not necessarily result from a direct action of dopamine: Boyeson and Feeney (1990) found that blocking the conversion of dopamine to noradrenaline by the inhibition of dopamine beta-hydroxylase coupled with the administration of dopamine abolishes its recovery-enhancing effect in rats with unilateral sensorimotor cortex ablations. Whether or not noradrenaline may play a more direct role compared with its precursor dopamine in motor recovery after sensorimotor cortex injury remains to be elucidated.

A single dose of the selective serotonin reuptake inhibitor (SSRI) paroxetine may increase motor dexterity in healthy subjects, which is accompanied by enhanced neural activity in the primary sensorimotor cortex and supplementary motor area (SMA) as revealed by functional magnetic resonance imaging (Loubinoux et al., 2002). Repetitive administration of paroxetine over 30 days has been shown to increase finger tapping frequency and to enhance electrophysiological indication of intracortical facilitation (ICF) measured by TMS in healthy subjects (Gerdelat-Mas et al., 2005; Loubinoux et al., 2005). A recent study also showed that citalopram, another SSRI, may improve dexterity in chronic stroke patients (Zittel et al., 2008). In contrast to
noradrenergic stimulation, however, the SSRI fluoxetine exerts no beneficial effect on motor recovery in rats with ischemia (Windle and Corbett, 2005). Furthermore, a study in patients with major depression (Hegerl et al., 2005) showed greater beneficial effects of RBX on motor function (increased velocity of rapid hand movements) than the SSRI citalopram. These findings could point to a more relevant role of the adrenergic system for modulating motor performance.

**Motor system and noradrenergic stimulation**

Pharmacological experiments with rats demonstrated that stimulating the noradrenergic system with RBX dose-dependently reduced immobility time in the forced swimming behavioral despair test (Wong et al., 2000). Studies with healthy human subjects suggest that noradrenergic stimulation may improve motor abilities related to gross motor skills (e.g., of proximal muscle groups) but not fine motor skills (e.g., finger movements): Using RBX, Plewnia et al. (2004) observed improved learning of a fast elbow flexion task (gross motor learning), but not in learning new finger sequences (fine motor learning, Plewnia et al., 2006) or in replicating an overlearned finger sequence (Plewnia et al., 2004). Likewise, Lange et al. (2007) did not observe changes in learning a complex finger lifting task when subjects were stimulated by RBX. Note that all these studies focused on RBX effects which potentially enhance motor learning (i.e., use-dependent effects). Most of the studies cited above especially focused on use-dependent improvements and motor-learning effects for (isolated) finger movements mediated by RBX. The only study reporting a positive effect of RBX on motor learning found effects after a training period of about 12 min (Plewnia et al., 2004). However, none of the studies reported immediate effects of RBX on motor (learning) performance with respect to finger movements. By contrast, Experiment I of the present study was not designed to specifically investigate training effects influenced by RBX over time. Rather, we employed a battery of different (visuo-)motor tasks
to test putative RBX effects on motor performance also including whole arm movements and hand–object or hand–tool interactions. Consistent with the studies that failed to demonstrate a RBX effect for speeding up finger movements in healthy subjects (be it after some minutes of practice or immediately as inferred from the pictorial material provided in Plewnia et al., 2004, 2006), we found no changes in index finger tapping frequency when healthy subjects were stimulated with RBX. Likewise, rapid pointing movements were not significantly faster when subjects had received RBX. The latter task showed a strong learning component compared with baseline performance, which was not different between RBX and placebo (cf. Table 3.1.1).

By contrast, the statistical analysis showed that some tasks showed selective improvements of task performance following RBX over and above the general training effects as observed in the placebo conditions. These visuomotor tasks, namely the joystick task, the wire-guidance task and the object-lifting task, all require a precise control of hand movements for object/tool interaction. Interestingly, also the task studied by Plewnia et al. (2004) required hand–tool interactions for the elbow-flexion task showing improvements in performance under RBX. In all these tasks, movement speed was significantly enhanced when subjects were stimulated with RBX. In contrast to the effects reported by Plewnia et al. (2004), our results showed a more or less immediate effect on visuomotor performance. However, the individual improvement rates (Table 3.1.2) revealed that not all subjects responded equally to RBX stimulation. We can only speculate why such differences in the response to RBX may have occurred: For example, subjects using different strategies to perform the visuomotor tasks probably recruit different cortical networks (Iaria et al., 2003; Nadeau et al., 1998) which in turn may be differentially modulated by RBX. Another possible explanation for the differences in response strength might lie in different genetic backgrounds. The impact of genetic polymorphisms on differences in behavioral responses
following pharmacological stimulation was recently demonstrated for the dopaminergic system in humans (Klein et al., 2007). As genetic polymorphisms have also been identified for the human noradrenergic system (Heinonen et al., 1999; Svetkey et al., 1996), analysis thereof might yield a better understanding of the effects induced by noradrenergic stimulants such as RBX.

**Noradrenergic stimulation, attention and optimal performance**

Given the results of the present (behavioral part of Experiment I) and other studies investigating the effects of RBX in both healthy subjects and patients, the improvements in task performance for visuomotor tasks could in principle also be related to enhanced attentional processing, especially as the locus coeruleus (LC) – which is the major source of noradrenaline in the cortex – plays a critical role in arousal by facilitating information processing of relevant or salient stimuli (Berridge and Waterhouse, 2003). Electrophysiological studies showed that the phasic activity of the LC is related to the behavioral responses in tasks with focused attention (Clayton et al., 2004; Rajkowski et al., 2004), while tonic activity of the LC, which is related to arousal, has an inverted U-shape relationship with task performance (Aston-Jones et al., 1999). These observations imply that an appropriate state of arousal might facilitate the task-related phasic discharge of the LC, and thereby improve behavioral responses. Studies in rats demonstrated that RBX administration interferes with the discharge rate of LC neurons (Wong et al., 2000). However, Plewnia et al. (2006) tested the effects of RBX upon various parameters of attention in a visual detection task in healthy human subjects and found no effects on simple motor reaction times, error rates or signal detection sensitivity. In line with these results, we did not find changes in the reaction times as derived from the computerized joystick task (i.e., the time from stimulus onset to the beginning of the joystick movement). Furthermore, the rapid horizontal finger pointing task which also relied on visual feedback
information and visuospatial attention was not significantly influenced by RBX. Likewise, the cardiovascular parameters did not reveal a change in heart rate or blood pressure as unspecific surrogate parameters for vigilance (Varri et al., 1994). Nevertheless, a more extensive testing of the effects of RBX on vigilance and reorienting is needed in the future for a better understanding of the task-specific actions of this drug.

Motor recovery after brain injury and the noradrenergic system

Administration of amphetamine has been shown to enhance recovery of function in rats and cats with unilateral ablation of the motor cortex (Feeney et al., 1982; Hovda and Fenney, 1984). Furthermore, blocking adrenoceptors by prazosin – a selective alpha-1 receptor antagonist – after the animals had fully recovered re-instated motor deficits (Stibick and Feeney, 2001). In (human) stroke patients, similar effects of noradrenergic stimulation have been observed: Amphetamine (Crisostomo et al., 1988; Walker-Batson et al., 1995) and the NA precursor L-DOPS (Miyai et al., 2000; Nishino et al., 2001) paired with physical therapy significantly improved motor recovery from hemiplegia. The specific effects of NA stimulation on motor behavior are, however, still under debate. Due to the technical limitations in studies reporting amphetaminergic actions (i.e., often small sample size with n < 5; no blinding of studies), two recent Cochrane review metanalyses (Martinsson et al., 2007; Martinsson et al., 2003) requested confirmation of the effects of amphetamine-like drugs in randomized controlled trials with larger sample sizes. Furthermore, amphetamine increases NA levels as well as dopamine (DA) and – at higher concentrations – serotonin (5-HT) levels by both enhanced release of neurotransmitters from synaptic vesicles and blocking of reuptake transporters (Azzaro and Rutledge, 1973). Accordingly, as amphetamine has actions on multiple neurotransmitter systems, specific statements about the amphetamine effects and the associated neural processes remain difficult. In addition, amphetamine has serious potential
cardiovascular side effects (e.g., induction of myocardial ventricular fibrillation or cerebral ischemia), thereby disqualifying its use in patients with cerebrovascular disease.

In the experiments of the present study, we used the highly selective noradrenaline reuptake inhibitor reboxetine (Wong et al., 2000) to specifically modulate noradrenergic influences. We observed that RBX significantly enhanced index finger tapping frequency and grip power of the paretic hand confirming the findings of a previous study: Zittel and colleagues (2007) also found that RBX compared with placebo induced an increase of tapping speed and grip strength of the paretic but not the unaffected hand after 1 h of physiotherapy. Interestingly, in healthy subjects, RBX did not affect tapping performance (Plewnia et al., 2004; behavioral part of Experiment I), and also the unaffected hand of stroke patients did not improve under RBX. These findings indicate that RBX does not improve tapping performance per se but rather enables a better control of the underlying neural mechanisms in disturbed networks resulting from stroke. The missing effects on the finger tapping task in healthy subjects could also result from a “ceiling” effect. The performance was already at its possible maximum, leaving no space for improvement.

4.2.2 NA-modulated neural networks engaged in visuospacial attention and motor control in healthy subjects

The connectivity analysis suggested a preferred flow of neural information from V1 over IPS to premotor and motor areas (Figure 3.1.5 & Figure 3.1.6), which is in good accordance with data derived from studies in nonhuman primates (Rizzolatti et al., 1997). The data showed enhanced influences of right IPS on right V1 under RBX stimulation. Such a top-down mechanism could explain the higher BOLD activity observed in right V1 compared with PBO (Figure 3.1.3; left V1 activity was much less enhanced under RBX and
only significant at uncorrected thresholds). The IPS is, however, not only engaged in visual attention (Corbetta et al., 2008; Nobre et al., 1997; Thiel et al., 2004), but also in visuomotor intention (Rushworth et al., 2003) and online control of movements (Eskandar and Assad, 1999; Grefkes et al., 2004). Our results suggest that the stronger implementation of right frontoparietal areas into the visuomotor network subserving joystick movements may have reduced the computational load posed onto the left hemisphere. In macaques, medial intraparietal cortex (area MIP) is engaged in planning and execution of reaching movements (Colby, 1998), and is strongly connected to the dorsal premotor cortex (Rizzolatti et al., 1998). Medial IPS is supposed to transform sensory (e.g., visual, auditory) target information into a common eye-centered reference frame which can be “read out” by the motor system independent of the type of action planned (Cohen and Andersen, 2000; Cohen and Andersen, 2002). Therefore, stronger activation of intraparietal cortex mediated by RBX stimulation might reflect enhanced engagement of transformation processes facilitating the integration of visual information into planned motor programs (i.e., goal-directed joystick movements) (Astafiev et al., 2003; Grefkes and Fink, 2005; Rushworth et al., 2001).

Although it is tempting to conclude that the critical neural correlate for improved task performance is the human homologue of area MIP, we can not make such a clear anatomical statement as also the human homologue of the LIP area is found on medial IPS in humans (Grefkes and Fink, 2005; Koyama et al., 2004). This area is involved in the transformation of (visuo-) spatial coordinates in saccadic eye movements (Andersen, 1995; Snyder et al., 2000), and also projects to superior frontal cortex, that is, the frontal eye fields (FEF) which are located slightly rostral to the reaching related neurons in dPMC (Boussaoud et al., 1998; Schall and Thompson, 1999). In a more conceptual framework, the FEF is thought to transform visual signals into motor commands (i.e., saccades), hence subserving similar properties as hand/arm related neurons in dorsal premotor cortex (Schall and Thompson, 1999;
Schubotz and von Cramon, 2003). However, cell recordings in macaques demonstrated that more than half of FEF neurons can be modulated by hand position signals (Boussaoud et al., 1998; Thura et al., 2008), which may indicate that this region has an important role beyond saccade programming, for example, in mediating visual salience and spatial attention for the control of hand and eye movements (Thompson and Bichot, 2005). Although we cannot exclude that changes in eye movements might have played a role for the BOLD signal increases observed under RBX stimulation, the strong lateralization of activity to the right hemisphere and the asymmetric changes in interhemispheric connectivity speak against a purely saccade related effect: Both saccades and also the suppression of eye movements typically show strong bilateral activations of the frontal eye fields (Connolly et al., 2002; Corbetta et al., 1998; Paus, 1996). Furthermore, the faster joystick movements under RBX were not associated with faster reaction times in starting the joystick movements after target onset. Hence, although we cannot rule out differences in eye movements between the RBX and PBO session, the missing effects on reaction times imply that target selection and control of saccades might not have played a dominant role for the neural effects observed. We rather suggest that the enhanced influence of right IPS onto the right FEF/dPMC region mediated by RBX may reflect the promotion of an interaction between eye- and hand-related neurons for the planning and execution of visually guided joystick movements (Boussaoud et al., 1998; Thura et al., 2008). Such a view is consistent with data showing that also human oculomotor areas in IPS and FEF are involved in pointing preparation and execution (Astafiev et al., 2003; Simon et al., 2002). It remains, therefore, difficult to separate the specific contributions of different attentional mechanisms to the joystick task. Andersen and Buneo (2003) also emphasize the extremely similar coding strategies of the reaching and saccade related areas in IPS suggesting that both regions (MIP, LIP) are parts of a single network for the purpose of coordinating hand and eye movements, and which
might both have been activated by the current experiment.

4.2.3 Neural correlates of NA improved motor performance in stroke patients

**RBX-mediated changes in neural activity**

Enhanced finger tapping frequency under RBX was associated with a reduction of overactivity during movements of the paretic hand, especially in ipsilesional vPMC, SMA and cingulate cortex (Figure 3.2.3 & Figure 3.2.4). This finding is compatible with other studies reporting that in stroke patients improvements in motor functions were associated with a decrease of task-related overactivity (Calautti et al., 2001; Marshall et al., 2000; Ward et al., 2003). A recent meta-analysis of human imaging data suggests that both SMA and vPMC constitute key motor areas for performing finger tapping tasks similar to that used in the present study (Witt et al., 2008). Studies in monkeys showed that these areas have extensive projections to M1 (Dum and Strick, 2005a) and, therefore, might play an important role in motor recovery (Dancause et al., 2005; Frost et al., 2003), e.g., by facilitating the motor output of M1 neurons through corticocortical projections (Shimazu et al., 2004). The finding that the normalization of overactivity also depended on the integrity of the corticospinal tract (CST) underpins its importance for reorganization and functional recovery after stroke (Newton et al., 2006; Ward et al., 2006).

Improvements in tapping performance were associated with reduced neural activity in key areas of the motor system in both hemispheres (Figure 3.2.2). In contrast, in the absence of a specific intervention, increases in tapping frequencies are typically paralleled by a steady increase in task-related BOLD signal in both healthy subjects or stroke patients (Hayashi et al., 2008; Riecker et al., 2010). We, therefore, propose that the reductions in movement-related activity under RBX might be caused by more efficient interactions among the motor areas, e.g., by stronger neuronal coupling.
(Grefkes et al., 2009). A recent study on motor learning showed that less
attentional control after movement automatization was accompanied by
decreases in neural activity but increases in effective connectivity in
task-related cortical and subcortical motor areas, suggesting a more efficient
neural coding of movement (Wu et al., 2008). Similar processes could underlie
the findings observed in the present study.

In addition to changes in “classical” motor areas, RBX stimulation also
yielded decreases in more “cognitive” regions such as temporal cortex or
DLPFC. Neuroimaging studies showed that these areas are typically involved
in tasks relying on motor learning (Seidler et al., 2006). Here, practice-induced
improvements in task performance are typically associated with a reduction of
neural activity in fronto-temporal areas, probably due to less cognitive effort for
practised tasks (Remy et al., 2008; Seidler and Noll, 2008). Similar processes
might explain the reductions in BOLD signal observed for areas in temporal
and prefrontal cortex when patients were stimulated with RBX, i.e., reduced
engagement of motor control areas due to improved motor abilities.

**Effects of NA on cerebral networks**

We observed that enhancing noradrenergic influences in stroke patients
induced a rearrangement of the functional network architecture. Specifically,
the influence of ipsilesional SMA on ipsilesional M1 was significantly enhanced
after RBX administration compared with PBO (Figure 3.2.6), and correlated
with the tapping performance of the affected hand (Figure 3.2.5C) but not with
tapping performance in healthy subjects. Such a difference indicates that in
stroke patients disturbed SMA-M1 interactions might contribute to the motor
deficits of the paretic hand. As we found a similar SMA-M1 “hypoconnectivity”
also in a different sample of patients performing a different motor task (hand
clenching movements) (Grefkes et al., 2008b), a general dysfunction of this
connection is likely to constitute a relevant factor for stroke-induced motor
impairments. Therefore, the increase in coupling strength of ipsilesional
SMA-M1 under noradrenergic stimulation could represent a critical factor mediating behavioral improvements at the stroke-affected hand.

### 4.2.4 Mechanisms underlying NA-modulated functional network

The data suggest that NA modulated a task-related functional network and increased interregional connectivity between regions. Accordingly, the question arises: How may NA exert these effects?

#### 4.2.4.1 Effects of NA on synaptic plasticity

Previous studies have extensively investigated the effects of NA on plasticity of the visual cortex. After monocular occlusion in a “critical period” (1-4 months of age) of kitten, binocularly responding neurons in the visual cortex begin to respond dominantly to the stimuli from the unclosed eye. When forced to use only the previously deprived eye, the kittens behave as if they were blind. This is named ocular dominance plasticity (Wiesel and Hubel, 1963). Depletion of NA in kitten visual cortex by 6-hydroxydopamine (6-OHDA), a neurotoxin destroying noradrenergic terminals, abolished ocular dominance plasticity, while local infusion of NA in kitten visual cortex enhanced ocular dominance plasticity (Imamura and Kasamatsu, 1991; Kasamatsu and Pettigrew, 1976; Kasamatsu et al., 1979; Pettigrew and Kasamatsu, 1978). In addition, NA may also mediate the induction of LTP in the hippocampus. LTP is a long-lasting enhancement of signal transmission between two neurons that results from coincident activity of pre- and post-synaptic elements, which reflects synaptic plasticity, and is suggested to be the key mechanism underlying memory and learning (Cooke and Bliss, 2006). Pharmacological studies demonstrate that beta-adrenoreceptor activation may facilitate the induction of LTP (Gelinas and Nguyen, 2005; Schimanski et al., 2007; Thomas et al., 1996; Yamada et al., 2006), while inhibition of beta receptors prevents LTP (Katsuki et al., 1997; Kemp and Manahan-Vaughan, 2008), suggesting
Discussion

that NA is a key factor for inducing plasticity. Studies at the molecular level provide more information on how this rapid modulation (within 2 h of administration of drug in the present thesis) happens. For example, in vitro slice experiments have provided evidence that NA facilitates synaptic plasticity by enhancing NMDA receptor-mediated response components (Broecher et al., 1992; Kirkwood et al., 1999). NA may increase the probability of activating NMDA receptors by modulating membrane K⁺ conductance. It has been shown that NA, through beta receptors, reduces K⁺ conductance and increases inward Na⁺ currents in motoneurons of cat sensorimotor cortex (Foehring et al., 1989). Reduction of K⁺ conductance, in turn, increases the amplitude of depolarizing synaptic responses, and thus facilitates excitatory input to reach the threshold of synaptic modifications.

4.2.4.2 NA mediated plasticity within M1

Several TMS studies with human subjects demonstrated that systemic pharmacological stimulation of the NA system may influence practice-dependent plasticity in M1 (Buetefisch et al., 2002; Meintzschel and Ziemann, 2006). Practice-dependent plasticity may be assessed in a thumb-movement paradigm (Classen et al., 1998): TMS of the motor cortex evokes a stereotypical movement of the thumb in a given direction. Then, subjects are asked to practice the movement of the thumb in the opposite direction. After practice for around 10 min, TMS of the motor cortex evoked the movement in the practiced direction but not in the original direction. This practice-dependent plasticity is attributed to a LTP-like mechanism, as the same drugs that can inhibit the induction of LTP may also suppress practice-dependent plasticity, e.g., by enhancing gamma-aminobutyric acid type A (GABAₐ) receptor-mediated inhibition (lorazepam) or blocking N-methyl-D-aspartate (NMDA) receptor-induced excitation (dextromethorphan) (Buetefisch et al., 2000). However, a drug that does not affect LTP induction
but only the gating of voltage-activated Na\(^+\) and Ca\(^{2+}\) channels (lamotrigine) has no discernable effect on the practice-dependent plasticity (Buetefisch et al., 2000). In several TMS studies, pharmacological modulation of the NA system revealed that agonists (amphetamine and methylphenidate) of NA enhanced practice-dependent plasticity (Buetefisch et al., 2002; Meintzschel and Ziemann, 2006), while antagonist (prazosin) reduced it (Meintzschel and Ziemann, 2006; Sawaki et al., 2003). For example, amphetamine accelerated the development and prolonged the duration of practice-dependent plasticity relative to placebo (Buetefisch et al., 2002). These results indicate that NA enables a rapid modulation of M1 plasticity (within 2 h of administration of drug), which might result from the mediation of LTP.

### 4.2.4.3 NA modulated neural network in the present study

In both experiments of the present thesis, we observed that RBX downregulated BOLD activity compared with PBO: (i) in contralateral M1 in healthy subjects when performing the joystick task and (ii) in bilateral motor cortex (especially in ipsilesional SMA and vPMC) in stroke patients when tapping the index finger of the paretic hand. Although the same brain activation pattern has already been observed in both healthy subjects and stroke patients, i.e., increased motor performance associated with reduced brain activation, the underlying neural mechanisms are still not fully understood (Calautti et al., 2001; Hlustik et al., 2004; Ward et al., 2003; Wu et al., 2004; Xiong et al., 2009). However, in contrast to the previous studies, in which reduced BOLD activity was induced after several weeks of practice or recovery, RBX reduced BOLD activity in contralateral M1 of healthy subjects and ipsilesional SMA and vPMC of stroke patients in around 2 h. This rapid modulatory effect could be induced either by the inhibition of alpha-2 receptor or by LTD-like mechanisms, as beta receptors may also help to induce LTD (Kemp and Manahan-Vaughan, 2008). Or, from a functional view, reduction in brain activity might be a consequence
of increased interregional connectivity, as the neural network increases its working efficiency, which in turn reduces the working load of individual component.

NA selectively modulated different neural networks in the two experiments of the thesis. In Experiment I, an attention network (right V1, IPS and FEF) was modulated by RBX, while in Experiment II, a motor network (especially in ipsilesional SMA and vPMC) was modulated. These results imply that the LC-NA system does not only modulate one particular functional/neuronal system, but has a more common effect on neuronal networks constituting a functional system. From a physiological perspective, NA, as a neuromodulator, may augment evoked responses by other inputs (either excitatory or inhibitory) while reducing spontaneous activity of targeted neurons (Waterhouse et al., 1980; Waterhouse et al., 1984). This suggests that modulation of neuronal responses to other inputs could be a prominent effect of NA. In this way, NA enhances the “signal-to-noise” ratio of targeted neurons in the cortex to increase their working efficiency (Gu, 2002; Servan-Schreiber et al., 1990). This characteristic of an activity-dependent modulation might answer the task-specific effects of NA: Only an “activated” neural network during a task may be modulated by NA. For example, in Experiment I, RBX significantly increased the activity of right IPS that was activated in the joystick task, but the same area was not necessarily activated in the control fist closure task, and thereby was less modulated by RBX. In addition, it has been suggested that the right hemisphere is dominant in reorienting attention, and particularly the dorsal frontoparietal network (including IPS, superior parietal lobule and FEF) is involved in selecting and linking stimuli and responses (Corbetta et al., 2008). This might explain why the activity of right V1, IPS and FEF as well as the interregional connectivity between them were increased by RBX compared with PBO in the joystick task. This attentional network enhanced by RBX further increased its influences on the contralateral motor cortex and thereby improved motor performance. In stroke patients, a previous study and the
present study showed that the coupling of ipsilesional SMA-M1 was correlated with the performance of the paretic hand, suggesting that the dysfunction of this connection is related to stroke-induced motor impairments (Grefkes et al., 2008b). Stimulating NA mechanisms significantly increased the coupling from ipsilesional SMA to M1 when patients moved the affected hand, and the increased coupling was accompanied by enhanced motor performance. Taken together, results of both experiments suggest that NA stimulation via RBX may increase interregional effective connectivity between regions. Enhanced efficiency within neural networks might, therefore, constitute the key mechanism underlying improvement in behavioral performance in healthy subjects and stroke patients under noradrenergic stimulation.

4.2.5 Open questions

In the present thesis, increased interregional connectivity was observed in both healthy subjects and stroke patients following noradrenergic stimulation, and it was associated with enhanced motor performance. However, the precise physiological basis for increased connectivity remains to be elucidated.

A common observation in both experiments was that BOLD activity of contralateral motor cortex was reduced by RBX even though motor performance was increased. The relationship between reduced brain activation and increased motor performance needs further clarification.

Although it has been suggested for a long time in animal models that stimulating the NA system may support recovery of motor function after brain injury, this hypothesis has not been extensively tested in humans. Several studies and the present thesis showed that a single dose of a drug stimulating the noradrenergic system may transiently improve the motor performance of the stroke-affected hand. However, whether drugs stimulating noradrenergic system may enhance motor recovery in clinical environment in a long-term range still needs investigation.
4.3 Conclusions

Stimulating the noradrenergic system may selectively modulate a functional network in both healthy subjects and stroke patients with motor deficits, and thereby improve motor performance. The increased interregional coupling by noradrenergic stimulation might constitute a key factor for enhancing motor performance.