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Behavioral characteristics and neural localization of sensorimotor adaptation

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by

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Affidavits following section 6 paragraph 2 No. 5 and 10 of the doctorate rules from the German Sport University Cologne, from September 29th 2004.

Hereby I declare: The work presented in this thesis is the original work of the author except where acknowledged in the text. This material has not been submitted either in whole or in part for a degree at this or any other institution. Those parts or single sentences, which have been taken verbatim from other sources, are identified as citations. I further declare that I complied with the actual "guidelines of qualified scientific work" of the German Sport University Cologne.

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Susen Werner

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Abbreviations

BA Brodmann Area – region of the cortex defined and then numbered by the German neurologist K. Brodmann in 1909. The nomenclature is based on the cell organization.

CNS Central Nervous System – comprises the brain, spinal cord and retina and coordinates each activity of the body.

PICA Posterior Inferior Cerebellar Artery – one of the three major arteries of the cerebellum.

RMSE Root Mean Square Error –quantifies the mean distance between two data series by

$$RMSE = \sqrt{\frac{\sum_{i=1}^{k} (\Delta X_i)^2 + \sum_{i=1}^{k} (\Delta Y_i)^2}{k}},$$

were ΔX_i and ΔY_i are the horizontal and vertical distances between the data series and k is the number of data points.

SCA Superior Cerebellar Artery – one of the three major arteries of the cerebellum.

TMS Transcranial Magnetic Stimulation – a non-invasive method to stimulate neurons of the brain by inducing weak electric currents.

Contents

1 Introduction

Motor control is an integral component of human life. One might even argue that communication via coordinated mouth movements and therefore all achievements of modern civilization would never have been possible without motor control. Human behavior is crucially bound to movement, which requires the central nervous system (CNS) to coordinate the contractions of over 600 muscles consistently in order to enable the movements of approximately 200 bones. Despite this challenge, we easily manage to perform smooth and precise movements even under constantly changing conditions. Everyday life provides countless demands to our motor system, and there are ubiquitous examples for the importance of motor learning. They range from the development of relatively broad skills such as walking to the emergence of more subtle motor skills such as typing this thesis. Furthermore, motor learning forms an intrinsic element in sports: Tripping movements in soccer, for instance, need to be adapted to the structure and condition of the ball or the playing field. Then again, all parts of our body are constantly changing during our life time due to growth (in the long run) or fatigue (in the short run), and the same movement will never require the exact same cooperation of muscles. Therefore the nervous system cannot rely on an invariant motor plan. Thus, it is obvious that motor learning is central for human development, and one can imagine the dramatic change in viability if motor learning is impaired.

This thesis deals with central research questions in the field of motor learning. Basic principles of human adaptability to changed visual environments are investigated and the involvement of explicit knowledge as well as the contribution of the cerebellum to motor learning are analyzed. The results give further insight into the location of motor learning within the CNS. Profound knowledge about motor learning principles and its neural localization are the basis for rehabilitation programs when motor learning capacities need to be revived after injury or maintained during illness and old age. In addition, it can help athletes to improve their motor learning skills. Last but not least, this knowledge represents a gateway to comprehending intelligence in brains and to producing intelligent machines which learn from experience.

Chapter 1 gives an introduction to one particular form of motor learning, namely sensorimotor adaptation, and presents common methods for its investigation. Then,

selected research results for *behavioral characteristics* as well as their theoretical implications are described (their neural correlates are discussed in more detail in Chapter 7.1). This part is followed by an introduction to the *neural localization* of sensorimotor adaptation focusing on the role of the cerebellum. For both parts, the topics are also discussed in greater depth within the introduction section of each study (Chapters 2.2, 3.2, 4.2, 5.2 and 6.2). Last but not least, the consequential objective for this thesis is outlined.

1.1 Sensorimotor adaptation

Sensorimotor adaptation includes all types of motor learning where an already existing motor behavior is altered. Although sensorimotor adaptation is a specific form of motor learning, it displays certain memory and learning phenomena that are similar to other types of motor learning, such as skill acquisition or sequence learning. Therefore, conclusions for memory or motor learning in general can be drawn from results from sensorimotor adaptation studies (Krakauer 2009).

The process of adaptation is induced by either intrinsic changes related to body growth (Held and Bossom 1961; Held 1965; Howard 1982; Bullock and Grossberg 1988), by spontaneous drift between the senses (Robinson 1976; Howard 1982), by compensation due to injury (Howard 1982; Jakobson and Goodale 1989; Goodale et al. 1990) or by extrinsic changes such as environmental variations (Bock et al. 2010). Whatever the type of change, it must first be perceived via sensory feedback. For example, a soccer player will feel with the help of his or her proprioceptive and visual organs that the same movement does not have the same effect when playing on artificial turf instead of lawn. Summing up, visual, acoustic or proprioceptive *feedback* plays a pivotal role in the process of sensorimotor adaptation.

This fact is widely used in sensorimotor adaptation research, where researchers deliberately change one or more feedback sources during the performance of standardized movements in a laboratory setting (Helmholtz 1867; Stratton 1897; Howard 1971). When first exposed to a change of feedback, i.e., a *distortion*, the subjects' behavior deteriorates followed by a gradual improvement until the movements are again performed accurately. All movements are recorded and can be analyzed and compared. This procedure was successfully applied for the analysis of sensorimotor

adaptation during walking (Morton and Bastian 2004), pointing to visual targets (Bock et al. 2003; Tong and Flanagan 2003), tracking a moving target (Bock et al. 2001; Mierau et al. 2009), grasping (Rand et al. 2004; Weigelt and Bock 2007) or saccadic eye movements (Bock et al. 2008; Xu-Wilson et al. 2009).

Various feedback distortions have been used in sensorimotor adaptation studies. For example researchers apply forces (mechanical distortions) to the performing limb in order to generate a mismatch between the intended and the sensed movement (Shadmehr and Mussa-Ivaldi 1994; Donchin et al. 2003). Also, either visual or acoustic feedback can be changed to induce a mismatch between the felt and the seen movement (Bock 1992; Seidler et al. 2001a) or the heard movement (Hawco and Jones 2010), respectively. This thesis only contains studies of *visuomotor adaptation*, i.e., the adaptation to visual distortions. These are commonly encountered in daily life, for example when we experience *reversals* of visual feedback by watching ourselves performing a movement in a mirror (where moving right/left leads to left/right movements of our mirror image). Also, *lateral shifts* of vision occur during observation of underwater objects. Another example are movements with a computer mouse, which are *amplified* into cursor movements on the screen. Furthermore, *rotation* of visual feedback appears during the control of an excavator, when movements of a lever lead to shovel movements in different directions.

Sophisticated variations of experimental conditions using the above mentioned movements and distortions can give insight into the behavioral mechanisms of sensorimotor adaptation, which again can lead to conclusions about the neural mechanisms underlying sensorimotor adaptation. For the direct exploration of neural mechanisms, the following research methods are used:

- In *clinical studies*, patients with clearly circumscribed lesions within the CNS perform experiments. Deficits indicate the contribution of the respective brain region to the performed task (Martin et al. 1996; Schaefer et al. 2009).
- An increasingly popular method is the use of *imaging techniques* such as functional magnetic resonance imaging or positron emission tomography. With these methods, brain activation is measured during the performance of the motor learning task (Imamizu et al. 2000; Diedrichsen et al. 2005).

- Also, *electroencephalographic activity* is used to analyze the temporal and spatial involvement of different brain regions in adaptation (Berndt et al. 2005)
- In a fourth method, brain regions are identified with the help of *transcranial magnetic stimulation* (TMS), or virtual lesions, applied over specific brain areas (Lee and van Donkelaar 2006; Hadipour-Niktarash et al. 2007).
- On the cellular level, *neurophysiological recordings of single-cell activity* are performed in animals (Georgopoulos et al. 1986; Paz and Vaadia 2009).

1.1.1 Behavioral characteristics of sensorimotor adaptation

Implicit and explicit processes in sensorimotor adaptation

Implicit motor learning refers to behavior which is performed automatically, non-intentionally (Frensch 1998) and without use of excessive mental concentration (Leonard 1998). While participants are unaware of implicit learning, explicit learning refers to conscious problem-solving. With the help of explicit learning, or declarative knowledge, task variables can be discovered (Green and Flowers 2003) and communicated (Leonard 1998). Especially more complex motor learning processes often contain explicit forms of knowledge acquisition (Kandel et al. 1995). Yet, the role of explicit knowledge in sensorimotor adaptation is under debate until today.

Implicit processes in sensorimotor adaptation were already observed about one hundred years ago: after removing the distortion, movements are again impaired and only gradually come back to normal behavior during a so called de-adaptation phase (Stratton 1897; Gibson 1933; Lazar and Van Laer 1968). Therefore it is safe to say that a lasting neural change, i.e., a *recalibration* (Howard 1971) or spatial realignment (Redding and Wallace 1996) of the CNS, occurs. More recently, recalibration has also been described by the concept of an *internal model* (Wolpert et al. 1995). This computational model describes the development of a motor skill based on the internal representation of the properties of our body and the environment. The model allows the anticipation of consequences of movement (forward model) as well as the determination of motor commands required to achieve a desired output (inverse model).

Since the beginning of research on sensorimotor adaptation, studies have revealed many characteristics of recalibration by means of aftereffect tests. The data shows that recalibration of sensory-to-motor transformation rules is relatively stable, showing retention even after up to a month (Shadmehr and Brashers-Krug 1997; Bock et al. 2001; Wigmore et al. 2002). Also, it is clear that recalibration is not task-specific, since it generalizes to untrained work regions (Bedford 1989; Shadmehr and Moussavi 2000), transfers to the other arm (Sainburg and Wang 2002) and to different movement categories (Abeele and Bock 2003). Furthermore no active movement is necessary for recalibration to occur (Cressman and Henriques 2010) and, above all, recalibration is not necessarily associated with an awareness of the distortion, i.e., recalibration develops *implicitly* (Kagerer et al. 1997; Abeele and Bock 2003; Buch et al. 2003; Klassen et al. 2005; Michel et al. 2007).

The remaining difference between aftereffect tests and adaptation data, for example partial transfer of adaptation (80%) to a different movement category (Abeele and Bock 2003), led to the common opinion that at least two distinct processes exist during the adaptation phase (Redding and Wallace 1993; Krakauer et al. 2000; Bock et al. 2001), one of them being recalibration. But what is the nature of the additional processes? If recalibration occurs implicitly, could the remaining processes include conscious or strategic, thus *explicit*, components? And could explicit knowledge therefore be proven to be beneficial to sensorimotor adaptation?

Recent research particularly confines to stating a *slow* process, recalibration, and a *fast* process (Smith et al. 2006; Kording et al. 2007; Ethier et al. 2008). The authors describe how the fast process responds strongly to performance error and quickly reduces it, but they restrain from referring to explicit or strategic processes. On the other hand, Redding and Wallace name the fast process *strategic control* and describe it by an agglomerate of implicit processes like feedback based corrections or associative learning and explicitly processed or intentional feed forward strategies (Redding and Wallace 1993; Redding and Wallace 1996; Redding et al. 2005). Accordingly, some other authors use the term “strategies” only for explicit feed forward processes (Welch 1978; McNay and Willingham 1998; Heuer and Hegele 2008a). Welch (1978), for example, proposes that explicit knowledge must develop as a basis prior to any cognitive strategies to develop. Following this reasoning, the existence of cognitive functions in sensorimotor adaptation might be an indication for existing

explicit knowledge. Already in the 1970s, Fitts and Posner suggested that early learning could be cognitively demanding (1967). This suggestion was confirmed by means of a dual-task paradigm which showed a high demand of resources pertinent to attention and spatial transformations in the early stages of sensorimotor adaptation (Eversheim and Bock 2001).

Furthermore, several studies showed age-related deficits during adaptation phase but not during aftereffect tests, which was explained by a concurrent age-related deficit in strategy formation (McNay and Willingham 1998), a deficit in cognitive factors (Fernandez-Ruiz et al. 2000), or a decay of executive functions (Bock and Girgenrath 2006). McNay and Willingham (1998) used "strategy formation" synonymously to "explicit knowledge"; however they did not directly test for it. Still, these results are a strong indication for the involvement of explicit knowledge during adaptation. This indication is backed up by the fact that older participants show evidence of impaired explicit processes (Craik and Jennings 1992). However, only one study did test explicit knowledge and sensorimotor adaptation at the same time in elderly subjects (Bock 2005). Again, the results show the same pattern of impaired adaptation but spared recalibration. Additionally, approximately 80% of the young subjects correctly described the nature of the distortion in an explicit knowledge questionnaire, as opposed to only approximately 8% of the elderly subjects.

Further hints for the involvement of explicit knowledge in adaptation processes comes from Shadmehr's laboratory (Hwang et al. 2006). In this study, depending on the starting position of their pointing movement subjects adapted either to clockwise or counterclockwise force fields. Those subjects who came to understand the force pattern showed better adaptation (i.e., a higher learning index, determined by adaptation and aftereffect data). The authors concluded that in force field learning the brain relies on implicit as well as on explicit learning systems. Similarly, it was shown that among patients with prefrontal cortical lesions, only those who acquired explicit knowledge of the distortion were also able to adapt (Slachevsky et al. 2003).

On the other hand, whenever subjects are instructed to use an explicit strategy during adaptation to a visual distortion, their strategy proves to be detrimental for adaptation (Mazzoni and Krakauer 2006). This study is described in more detail in the introduction of the first study (Chapter 2.2). Some researchers further argue that improved recalibration is observed when explicit knowledge is prevented by stepwise introduc-

tion of the distortion, e.g., without the occurrence of large movement errors and thus awareness of the change (Redding et al. 2005). Yet, studies using gradual adaptation yield contradictory results, some showing enhanced recalibration as measured by aftereffect test (Kagerer et al. 1997; Ingram et al. 2000; Michel et al. 2007) and some not (Klassen et al. 2005; Werner et al. 2009).

Summing up, there is increasing evidence for the involvement of explicit knowledge during sensorimotor adaptation. However, it is still under debate whether this explicit knowledge has a beneficial, neutral or detrimental effect on the adaptation process. This research question is investigated in the first study of the present thesis.

Adaptive processes in sensorimotor adaptation

Another basic question in sensorimotor adaptation research is whether adaptation to different distortions follows similar *processes*, where the term process is used in a descriptive way for the observed behavioral changes. After analysis, quantification and comparison of the behavioral processes, conclusions can be drawn about the underlying neural processes, or their internal representation, respectively. Similarity or disparity of adaptive processes can be examined via two different approaches. First, one can analyze the *effect of successive adaptation* to different distortions. Second, researchers compare the *characteristics of adaptive processes* to different distortions. In the following, research investigating adaptation via the two approaches is summarized.

During adaptation to *successive distortions* several effects occur simultaneously. On the one hand, an improvement of the subject's ability to adapt, i.e., *learning to learn*, was found (Bock et al. 2001; Seidler 2004). This effect indicates an increasing plasticity within the CNS after frequent adaptation. On the other hand, the so called *consolidation effect* suggests that motor memories go from fragile to protected states over time. This effect was shown in some (Brashers-Krug et al. 1996; Shadmehr and Brashers-Krug 1997; Krakauer et al. 2005) but not all studies on successive sensorimotor adaptation (Caithness et al. 2004), and it remains debatable (Bock 2003; Bock et al. 2003; Caithness et al. 2004). However, both results do not shed any light on the question of similarity or disparity of adaptive processes.

In a further series of studies it was argued that impairment, or interference, of adaptation to a second distortion after adaptation to a first one suggests that both distortions

are based on common processes, since they demand the same resources in the working memory (Krakauer et al. 1999; Wigmore et al. 2002). However, an overview of the existing literature reveals that the effect of one distortion *A* to a subsequent distortion *B* explicitly depends on the *direction* of feedback. When exposed to distortions acting within the same direction (for example first to a small rotation and then to a larger one), the subjects show an improved second adaptive process (Abeele and Bock 2001b; Wigmore et al. 2002; Bock et al. 2003). Contrarily, successive adaptation to rotations/force fields in opposite directions leads to an impaired adaptation process (e.g., Brashers-Krug et al. 1996; Wigmore et al. 2002; Caithness et al. 2004; Miall et al. 2004). The same holds for distortions that differ in their nature (e.g., mechanical versus visual) or their coupling to the hand (e.g., position versus velocity dependent): facilitation is observed for distortions acting in the same direction (Thomas and Bock 2010), while opposite directions again lead to impairment (Tong et al. 2002; Bays et al. 2005). Subsequent distortions in independent directions consequently lead to independent adaptation (Krakauer et al. 1999). This sequence of studies led to the conclusion that adaptation to different distortions might be based on common processes (Thomas and Bock 2010) and that the adaptive behavior of the first distortion is gradually modified during the second adaptation phase (Abeele and Bock 2001a; Bock et al. 2003).

Instead of disentangling the different effects of successive adaptation, one can also compare the *characteristics* of different adaptive processes. This method is used in Study 2 and 3 of the present thesis. Also, Lackner and Dizio (1994) compared the characteristics of adaptation to force fields to adaptation to the Coriolis force, as experienced by subjects when performing pointing movements during passive body rotation. Because of considerable variations in the adaptation processes, such as the rate of adaptation and the perception of the force, the authors argued in favor of a fundamental difference in terms of adaptation mechanisms. According to them, adaptation to force fields leads to the development of a new internal representation, while adaptation to a Coriolis force corresponds to learning of an external tool. However, the difference in adaptation rate can easily be explained by the deviating number of target points in the two adaptations (Krakauer et al. 2000).

Accordingly, on should bear in mind that differences in behavioral processes are not necessarily caused by differences in terms of the distortion but could also be due to

methodical differences. The approach to compare the characteristics of different adaptive processes is therefore most suitable when the compared distortions can be tested under similar conditions. As a consequence, the comparison of adaptive processes under mechanical versus visual distortions has preferably been studied during successive adaptation as described earlier, or, even better, with the help of imaging studies. For *visual distortions*, however, some comparisons have been made. In one study (Krakauer et al. 2000) subjects performed pointing movements while adapting either to an altered gain or to a rotation of visual feedback. The results show several differences in terms of the adaptation processes:

- The subjects learn the new gain at the same rate, independent from the number of target distances. In contrast, learning the rotation is less complete and takes longer when more target directions are used.
- After successful gain adaptation, a learning transfer to untrained target distances *and* directions is found, while rotation adaptation only transfers to untrained distances. These results are in line with the finding that amplitude and direction are distinct parameters of motor control and planning (e.g., Gordon et al. 1994; Rossetti et al. 1995; Vindras et al. 2005).

In a further study the comparison of different reversals of visual feedback revealed a slower adaptation process under up-down reversal than under left-right reversal (Caselli et al. 2006). However, the differences are small due to a high variability, and the authors associate this difference to the frequent exposure to distortions similar to a left-right reversal in everyday life. Already in 1989, Cunningham et al. conducted an extensive study comparing adaptation to several rotation angles (0°, 45°, 90°, 135° and 180°), to left-right and to up-down reversals of visual feedback. The authors found no distortion specific decrease in adaptation, but state a consistent pattern of the visual-to-motor conversion mechanism, according to which all distortions require the selection of new movement axes and/or directions. From this mechanism, they draw the conclusion of the existence of a general, or common, adaptation process. Yet, no detailed analysis of the data was shown to support this interpretation.

Today, the two mentioned distortions, namely rotation and reversion of visual feedback, are commonly used in sensorimotor adaptation research. Under adaptation to rotated visual feedback an interplay of a gradual process which slowly rotates sub-

jects' responses by up to +/-90°, and a discrete process which changes the responses by means of axis inversion has been shown (Abeele and Bock 2001b). However, it is still not clear by which adaptive processes the learning of visual reversal is achieved, and whether responses to both distortions follow common principles. Study 2 and 3 of the present thesis are aimed at clarifying this point.

Generalization in sensorimotor adaptation

Another essential question in sensorimotor adaptation research concerns the generalization or transfer of sensorimotor adaptation: Does adaptation to a specific distortion transfer to different body segments, different movements or different workspaces? Apart from the ethical component (scientists do not want their subjects to be impaired in their movements after participating in an experiment) an answer to these questions can give deep insight into the nature of motor learning and the involved brain structures. In the following, selected studies on transfer of sensorimotor adaptation are described.

Intermanual transfer, i.e., transfer from *one arm* to *another*, has been investigated in quite a few studies (e.g., Taub and Goldberg 1973; Imamizu and Shimojo 1995; Wang and Sainburg 2004; Wang and Sainburg 2006). However, it is still unclear whether sensorimotor adaptation is stored in an effector-specific memory. Apart from intermanual transfer, adaptive behavior can be transferred from *shoulder* to *wrist pointing movements* (Seidler et al. 2001b), from *visual* to *auditory targets* (Harris 1963; Michel et al. 2007) and from *pointing movements* to *saccades* (Bock et al. 2008). These results indicate that at least parts of the adaptive process are centrally located and can be accessed by different subsystems such as joints, end-effectors or sensory modalities.

Another series of experiments investigated whether adaptation to one distortion transfers to *different movements* or tasks using the same end-effector. In one study, subjects first adapted to a 30° rotation of visual feedback while doing pointing movements, second to a -30° rotation while doing either tracking, figure-eight drawing, or pointing movements, and third again to a 30° rotation while doing pointing movements. Interference was only observed for those subjects performing the identical task while experiencing opposite rotations (Tong and Flanagan 2003). The authors explain their results by the existence of task specific memory resources. How-

ever, it is also possible to assume a flexible complex system with transfer not being obligatory but possible.

In fact, several additional studies showed transfer from pointing to circular movements during force field adaptation (Conditt et al. 1997), or from pointing to tracking movements and vice versa during visual rotation adaptation (Abeele and Bock 2003; Bock 2005; Bock and Girgenrath 2006). It is remarkable that Abeele and Bock (2003) found less transfer from tracking to pointing than from pointing to tracking movements. This sort of asymmetric transfer was also shown very recently by Ikegami (2010): Adaptation to a visual rotation is almost completely transferred from discrete to rhythmic pointing movements, but not vice versa. Both studies might be explained by taking into consideration that discrete pointing movements include components of feed forward control (Jordan and Rumelhart 1992) as well as feedback or online control (Kawato 1990; Gomi and Kawato 1993), whereas tracking or rhythmic pointing movements are mainly controlled by online control. Thus, if feed forward components are not trained in one condition (tracking, rhythmic pointing), they cannot be transferred to the other one.

Marotta et al. (2005) further investigated the transfer from identifying different orientations to pointing to different locations under reversal of visual feedback. They found an independent recalibration of the "identify orientation" and the "point to location" systems, i.e., no transfer between the two conditions. The authors interpreted their results as two sensorimotor adaptation models occurring in parallel. This notion of parallel systems suggests a concatenated series of recalibrations within parallel neural streams (Henriques et al. 1998; Colby and Goldberg 1999).

The results of the experiments investigating transfer between different tasks indicate that the more similarly different movement tasks are planned and executed the more likely adaptive behavior is transferred between them. Based on this premise, it is striking how even the identical movement, e.g., pointing movement, sometimes transfers to untrained targets (e.g., Bock 1992) and sometimes does not (e.g., Imamizu and Shimojo 1995). One of the aims of the present thesis is to elucidate this topic (Studies 1, 2 and 3). A meta-analysis of the available literature reveals that after adaptation to visual rotation, transfer can be found whenever untrained targets require a new movement amplitude (Bock 1992; Goodbody and Wolpert 1998; Krakauer et al. 2000), while it does not occur when the targets require a new *movement*

direction. As for the second case, several recent studies report decaying transfer with increasing angular distance of the trained targets (Imamizu and Shimojo 1995; Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Pine et al. 1996; Krakauer et al. 2000; Wang and Sainburg 2004; Wang and Sainburg 2005). These studies suggest a (direction wise) *local*[1] way of adaptation based on directionally tuned modules. In contrast, adaptation to reversed vision has traditionally been assumed to initiate a *global* recalibration process (Stratton 1897; Harris 1965; Welch 1986); transfer to untrained directions, however, has never been measured. Likewise, adaptation to altered gain is usually achieved globally (Bock 1992; Krakauer et al. 2000), but local adaptation has also been shown under specific practice conditions (Heuer and Hegele 2008b). Thus, it is still under debate whether visuomotor adaptation is a local phenomenon specific for trained targets, or rather a global phenomenon generalizing across all target directions.

1.1.2 Neural localization of sensorimotor adaptation

The human brain consists of approximately 100 billion neurons or 100 trillion synapses. Now, which of them are involved in sensorimotor adaptation? Obvious candidates are the motor systems, which are shown schematically in Figure 1. Even within textbooks, however, there is no full consensus about their components. Some authors exclude the spinal cord and the brainstem (Carpenter 1996), others again include the cingulate motor cortex (Mast et al. 2007), the basal ganglia (Carpenter 1996), the parietal cortex or even the muscles themselves (Leonard 1998). Also, the respective sensory systems could be considered, since adaptation is nothing but an altered transformation of sensory inputs into motor outputs.

Numerous studies tried to localize sensorimotor adaptation with the help of *imaging techniques* (e.g., Shadmehr and Holcomb 1997; Imamizu et al. 2000; Girgenrath et al. 2007; Grafton et al. 2008). Most studies found a widely distributed neural network of adaptation related brain activity. However, size and location of this network differ between studies. These deviations can be assumed to occur due to the different

[1] The term *local* in a strictly mathematical sense would imply recalibration to occur only at the trained target. There could be transfer at nearby locations that are mistaken for this target, with the probability of confusion decreasing with further distance in direction. But since transfer was observed even at 90° separation (Krakauer et al., 2000), the term *local* is here used in an eye-catching way describing a *regional* process.

ways of measuring adaptation related activity. In fact, brain activity during a control condition like watching successful trials of the task (Graydon et al. 2005), performing an eye movement task (Inoue et al. 2000; Floyer-Lea and Matthews 2004) or a movement task without distortion (Lang et al. 1988; Inoue et al. 2000; Krakauer et al. 2004; Graydon et al. 2005) was subtracted from the brain activity during adaptation. These control conditions differ from the original adaptation condition not only with respect to the absence of the adaptation process itself, but also with respect to the absence of movements as well as to the occurrence of performance errors. Yet, these errors could for example account for additional brain activity related to an increased muscular tone, raised alertness or corrective arm movements. A similar problem occurs when comparing activation of early versus late adaptation (Chapman et al.; Krebs et al. 1998; Luaute et al. 2009), since performance errors commonly diminish with advancing adaptation.

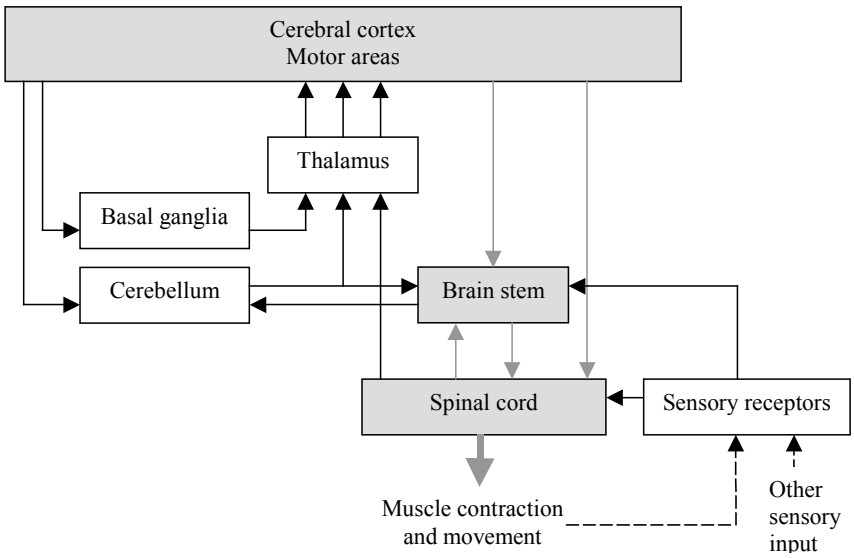

Fig. 1 Scheme of the motor systems (modified from Kandel et al. 1995). The motor areas of the cerebral cortex include the primary motor area (Brodmann Area (BA) 4), premotor cortex (lateral BA 6) and supplementary motor area (medial BA 6).

If only those studies are considered that use adequate control tasks (at least for part of the adaptation process) less activation was detected: adaptation to mechanical distortions leads to brain activity in the parietal lobe (Brodmann Area (BA) 7), premotor cortex of the frontal lobe (BA 6), prefrontal cortex (BA 46), occipital gyrus (BA 18), thalamus (all Shadmehr and Holcomb 1997) and cerebellum (Shadmehr and Holcomb 1997; Nezafat et al. 2001). Adaptation to visuomotor distortions only relates to

brain activity in the parietal lobe (BA 40/39) (Clower et al. 1996; Girgenrath et al. 2007), premotor cortex (BA 6) (Girgenrath et al. 2007) and cerebellum (Imamizu et al. 2000; Imamizu et al. 2003).

Grafton et al. (2008) further estimated the feed forward and feedback components of adaptation to a compensatory tracking task with the help of a state-space model, and they associated those components with brain activity: feed forward control therefore relates to activity in the inferior parietal lobe (BA 7/40), premotor cortex (BA 6), supplementary motor area (BA 6) and cingulate motor area (BA 5/24), whereas feedback control relates to brain activity in the posterior superior parietal lobe (BA 7/40) and premotor cortex (BA 6). Interestingly, cerebellar activity was only correlated to performance errors.

Instead of analyzing the magnitude of local activity, Tunik et al. (2007) chose a different approach: They examined changes of the network dynamics by focusing on the coherence of different brain regions. Their analysis reveals different functional interactions for different mechanical distortions: a cortical-basal ganglia network being associated to a velocity dependent distortion, and a cortical-cerebellar network to a position dependent distortion. Similarly, an investigation of functional connectivity reveals strong connections between the sensorimotor cortex, the anterior cerebellum as well as the temporal gyrus at the end of adaptation (Della-Maggiore and McIntosh 2005). Dividing the scanned voxels into clusters with similar spatial and temporal patterns (cluster analysis), yet another analysis revealed a decreasing activity in a fronto-parieto-cerebellar network during adaptation to reversed vision (Balslev et al. 2002).

Summing up, a great challenge in using imaging techniques for the localization of sensorimotor adaptation is to differentiate between brain activity related to adaptation and brain activity related to motor execution, for example error correction movements. A meta-analysis of the available literature reveals that there are differences - but also a marked overlap - between neural networks for adaptation to different distortions, especially concerning mechanical and visual distortions. Moreover, most studies found an involvement of the *premotor cortex*, the *parietal cortex* and the *cerebellum* in visuomotor adaptation. Consequently, the following section will elaborate on those three brain regions.

Further hints for the involvement of the *motor cortex including the premotor cortex* in sensorimotor adaptation comes from studies using TMS and clinical studies. Lee et al. (2006) showed a decreased adaptation rate and impaired recalibration during aftereffect tests when TMS disrupts the activity in the dorsal premotor cortex at the onset of every movement. Since TMS led to straighter movements and had no effect on a terminal feedback condition, the authors concluded that the premotor cortex contributes to online error correction. By contrast, no effect on adaptation was found when TMS was applied at the end of the movement (Lee and van Donkelaar 2006; Hadipour-Niktarash et al. 2007). Then again, applying TMS at the end of the movement led to a faster de-adaptation (Hadipour-Niktarash et al. 2007) or impaired retention (Richardson et al. 2006) when applied to the primary motor area, which indicates an involvement of this brain region in motor memory formation. However, a further study applying TMS to primary motor area did find unimpaired retention (Baraduc et al. 2004), so the topic remains controversial. The results of two clinical studies do not clarify the subject any further: frontal lobe lesions either led to impaired prism adaptation (Canavan et al. 1990; Patton et al. 2006; Scheidt and Stoeckmann 2007) or had no effect on adaptation (Welch and Goldstein 1972).

The involvement of the *parietal cortex* was also analyzed with the help of TMS. Della-Maggiore et al. (2004) showed impaired force field adaptation when TMS was applied on the posterior parietal cortex. Furthermore, the application of TMS led to a leftward shift in pointing during baseline movements as well as after adaptation to visuomotor reversal (Vesia et al. 2006). The authors concluded that TMS alters the output of the posterior parietal cortex downstream from the adaptive process, modifying it in motor coordinates. Moreover, since it is known that Alzheimer´s disease leads to anatomical changes (Braak and Braak 1991) and a reduction of the regional cerebral glucose metabolism in the parietal and frontal lobes (Mielke and Heiss 1998; Trollor et al. 2005), impaired adaptation for patients with Alzheimer´s disease would also confirm the involvement of the parietal cortex in sensorimotor adaptation. And in fact, three out of four studies testing adaptation in patients with Alzheimer´s disease did yield adaptation deficits compared to healthy control subjects (Weiner et al. 1983; Tippett and Sergio 2006; Tippett et al. 2007). In addition, event related lateralization of electroencephalographic activity also seems to affirm the involvement of the parietal cortex in adaptation to displaced vision (Berndt et al. 2005). Further-

more, Newport et al. (2006) showed impaired prism adaptation in a patient with bilateral posterior parietal cortex damage.

The brain structure whose role in adaptation has been most controversially discussed is the *cerebellum*. Ever since the theory of Marr, Albus and Ito, there has been an ongoing dispute about its involvement in motor learning (e.g., Llinas 1981; Thompson 1986; Lisberger 1988; Bloedel 1992). First proposed by Marr (1969) and later extended by Albus (1971) and Ito (1984), the so-called Marr-Albus-Ito theory is a prime example for deducting a functionality from a neural structure. In short, the theory suggests that one neuronal input projection (the climbing fiber) leads to a teaching signal that stimulates cerebellar processes to produce the correct output. Based on this theory, several computational models on cerebellar learning evolved (e.g., Eccles 1967; Jordan and Rumelhart 1992; Kawato and Gomi 1992; Miall et al. 1993; Haith and Vijayakumar 2009). More recently, Kawato and Wolpert (1998) developed the Modular Selection And Identification For Control (MOSAIC) model for sensorimotor control, which contains multiple pairs of forward and inverse models. The selection of the pairs is based on feedback as well as feed forward sensorimotor information, and they are all thought to reside in the cerebellum (Imamizu et al. 2003).

Despite the vast number of computational models on cerebellar learning, results from behavioral experiments remain controversial and the exact role of the cerebellum in motor learning is still unclear. Studies on different types of motor learning like vestibulo-ocular reflexes (Anderson et al. 2002), scaling of reflexes (Bloedel and Bracha 1997) or conditioning (Woodruff-Pak 1997; Timmann et al. 2000; Gerwig et al. 2003) do support the contribution of the cerebellum to motor learning per se. However, once the effects of sequence learning were separated from the concurrent changes in motor performance, no cerebellar activation could be associated with the learning experience in an imaging study (Seidler et al. 2002). Therefore, the cerebellum seems to contribute to performance modification rather than to learning itself for this type of motor learning. The same might hold for sensorimotor adaptation, one further type of motor learning. There is an ongoing debate in literature focusing on this topic, as is outlined in greater detail in the introduction of Study 4 (Chapter 5.2). It is striking that despite this debate, out of numerous clinical studies showing impaired adaptation in patients with cerebellar disease (Gauthier et al. 1979; Weiner et

al. 1983; Deuschl et al. 1996; Martin et al. 1996; Maschke et al. 2004; Diedrichsen et al. 2005; Tseng et al. 2007), only one distinguished between adaptation and performance deficits (Martin et al. 1996).

This study compares adaptation and motor performance in healthy control subjects and two groups of patients, one group with lesions within the area of the posterior inferior cerebellar artery (PICA), the other group with lesions within the superior cerebellar artery (SCA) area. The authors found PICA lesions to lead to adaptation deficits but intact motor performance. This is in sharp contrast to the findings of a second cerebellar lesion study, which shows an adaptation deficit following an SCA lesion (Pisella et al. 2005). Therefore, it has still to be clarified which specific parts of the cerebellum contribute to sensorimotor adaptation.

1.2 Research objective

The main objective of this thesis is to specify the location of sensorimotor adaptation within the CNS. For this purpose two approaches are chosen:

- Selected behavioral characteristics are investigated. These analyses promise not only to reveal basic principles of sensorimotor adaptation, but also to lead to a broader knowledge of the neuronal correlates of motor control.
- Clinical studies give direct insight into the neuronal location of sensorimotor adaptation.

A careful analysis of the existing literature revealed the following scientific questions and led to the five studies that form the basis of this thesis (see Table 1).

Research questions on the behavioral characteristics of sensorimotor adaptation

The first section of paragraph 1.1.1 showed how explicit processes or declarative knowledge are likely to be involved in sensorimotor adaptation. However, it has still been unclear whether they have a beneficial or a detrimental effect. This thesis therefore tries to further determine the role of declarative knowledge for sensorimotor adaptation. To this end, subjects were interrogated regarding the nature of the distortion after they adapted to a visual rotation. Adaptation and aftereffect data of correct responders were then compared to that of incorrect responders. This examination can provide further insights into a potential involvement of higher brain regions (such as

dorso-lateral prefrontal cortex) in the adaptation process, which are candidates for the involvement in explicit processes (Willingham 1998; Willingham et al. 2002).

The second section of paragraph 1.1.1 revealed that there are indeed common basic principles to very different distortions such as mechanical and visual distortions. However, it also became clear that there are even explicit differences between different visual distortions, for example adaptation to an altered gain leading to a more global recalibration than adaptation to rotated visual feedback. This thesis compares the adaptive processes caused by a rotation and a reversal of visual feedback. To clarify the issue, subjects performed pointing movements to targets presented in eight different directions during exposure to left-right reversed visual feedback. The direction of each response was quantified and the time course of those directions was separately analyzed for different targets throughout the adaptation phase. This data was then compared to the time course of directions under adaptation to visual rotations, which are known to be achieved by an interplay of gradual and discrete processes. If common principles emerge from this comparison, the results of numerous adaptation studies for visual rotation can easily be transferred to adaptation to visual reversal and vice versa. Furthermore, it can safely be assumed that similar brain regions are involved in both adaptation processes.

The last section of paragraph 1.1.1 gave a summary of the existing literature on generalization in sensorimotor adaptation. Here, one major research focus investigates whether adaptation to visual distortions is a directionally local or a global phenomenon. While adaptation to reversed vision and to altered gain is referred to as being global, several studies suggest that adaptation to visual rotations is based on directionally tuned modules. In this thesis, two approaches are chosen to scrutinize this topic:

- The effect of variable training, i.e., practice in all possible directions, is determined during adaptation to a visual rotation. Therefore, one group of subjects points at eight targets, and another group executes unconstrained arm movements throughout the workspace. If the specific condition of variable practice leads to improved adaptation and/or recalibration, a global adaptation process can be assumed and the local phenomenon found in earlier studies is not a rigid constraint of adaptation to rotations.

- Adaptation to left-right reversal, which, in the present study, requires a 180°, ±90°, or no change of response direction depending on target position, is compared to adaptation to rotations requiring the same adaptive change. A decrement of reversal adaptation can be attributed to a possible interference between neighboring modules. Furthermore, an analysis of pointing movements to trained and untrained directions under reversed vision is performed and this data is compared to the predictions of a simple Gaussian model of superposing neighboring modules. This investigation has the promise to reveal whether reversal adaptation is a global or local phenomenon.

Since neurons of several different brain regions are known to be directionally tuned, these analyses can provide knowledge into where the adaptation process is represented in the CNS.

Research questions on neural localization of sensorimotor adaptation

Paragraph 1.1.2 provided a review of neuro-imaging and clinical studies trying to localize sensorimotor adaptation within the CNS. Most imaging studies found brain activation in the motor cortex (especially the premotor cortex), the parietal cortex and the cerebellum during visuomotor adaptation. Further results of clinical as well as TMS studies mostly confirmed the involvement of motor and parietal cortices. A meta-analysis of the available literature revealed that there has been an ongoing dispute about the involvement of one particular brain structure in motor learning, namely the cerebellum. Although imaging and clinical studies as well as modeling approaches provide increasing evidence that the cerebellum plays an important role in sensorimotor adaptation, it is still not clear whether it participates in the adaptive process per se or steers motor performance as a prerequisite for adaptation. Furthermore, it remains to be determined whether different parts of the cerebellum play different roles during adaptation. Therefore, this thesis tries to elucidate the role of the cerebellum via two experiments:

- Adaptation to visual rotation *and* motor performance in a group of patients with cerebellar atrophy but without extra-cerebellar lesions are compared to a group of healthy control subjects. In addition, several indicators of adaptive success and motor performance are quantified, and a multiple regression

analysis of motor performance variables as well as one variable related to cerebellar integrity singles out the explanatory variables of adaptive success.

- Patients with lesions within either the PICA or the SCA territory and a group of healthy control subjects are tested on adaptation to visual rotation. As in the preceding experiment, adaptation and performance measures are quantified, compared and used in a multiple regression analysis. Furthermore, cerebellar lesion-symptom mapping using magnetic resonance imaging (MRI) subtraction analysis is performed in order to reveal cerebellar regions that show an overlap related to deficits in adaptation. These analyses might help to scrutinize the contribution of the posterior inferior and superior cerebellum to visuomotor adaptation.

Research questions on the behavioral characteristics of sensorimotor adaptation	
Does declarative knowledge have a beneficial effect on visuomotor adaptation?	Study 1
Are adaptation to rotated and to reversed visual feedback based on similar processes?	Study 2 & 3
Is visuomotor adaptation based on local or global processes?	Study 1, 2 & 3

Research questions on the neural localization of sensorimotor adaptation	
Are sensorimotor adaptation and/or motor control located within the cerebellum?	Study 4
Which part of the cerebellum plays a role in sensorimotor adaptation?	Study 5

Tab. 1 Outline of the main research questions of this thesis including the corresponding study number.

2 First study:
Effects of variable practice and declarative knowledge on sensorimotor adaptation to rotated visual feedback

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Reference

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2.1 Abstract

It has been shown before that sensorimotor adaptation to rotated vision is more generalized when subjects point at eight, rather than at four or less targets. Here we evaluate whether an even more variable practice has additional benefits. One group of subjects pointed at eight targets, and another group executed unconstrained arm movements throughout the workspace. We found no advantage of the latter group with respect to adaptive progress, persistence of adaptation without visual feedback, or transfer of adaptation to a new motor task. We therefore concluded that eight targets are sufficient to yield generalized adaptation. To determine the role of declarative knowledge for sensorimotor adaptation, subjects from both above groups were questioned regarding the nature of the distortion after they completed the experiment. We found that correct responders showed better adaptive progress, more persistence, but the same transfer as incorrect responders. We therefore concluded that the benefit of declarative knowledge is task-specific and short-lived, and is therefore probably related to strategic control rather than to an adaptive recalibration of the sensorimotor system.

2.2 Introduction

It is well established that the acquisition of a new motor skill is more efficient under variable than under constant practice, i.e., when subjects train several versions of the skill in intermixed order, rather than a single version repetitively. Thus, variable practice results in better retention of the trained skill, and in better transfer to completely new variants of the skill (McCracken and Stelmach 1977; Shea and Kohl 1991). These findings were interpreted as evidence that variable practice encourages the formation of generalized motor programming rules, while constant practice allows subjects to simply reiterate one or a few specific motor commands.

The advantage of variable practice seems to apply to sensorimotor adaptation as well. When subjects are exposed to rotated visual feedback while pointing at one, two, four, or eight targets, their speed of adaptation drops with an increasing number of targets, but transfer to unpracticed location improves with an increasing number of targets, reaching 100% when all eight targets are used (Krakauer et al. 2000). Thus, practice of one or a few different responses seems to support a quick but local form of adaptation, while practice of eight different responses results in a slower but more generalized form of adaptation. In fact, adaptation with eight pointing responses is generalized enough to yield substantial transfer even to a completely different movement category, namely, manual tracking (Abeele and Bock 2003; Bock 2005). One purpose of the present work was to determine whether adaptation becomes even more generalized when responses are not limited to a set of eight, but rather are unconstrained, thus allowing subjects to explore the distorted workspace in any desirable detail. Obviously, we cannot expect unconstrained practice to increase the transfer to unpracticed target locations, since transfer was already complete when eight targets were used (Krakauer et al. 2000). However, unconstrained practice could improve the speed and magnitude of adaptation, the persistence of adaptation after withdrawal of visual feedback, and/or its transfer to manual tracking.

The second purpose of our study was to evaluate the role of explicit processes for sensorimotor adaptation. Previous research has shown that the acquisition of new motor skills can be based on explicit processes, which are accessible to consciousness and verbal report, but also on implicit processes, which subjects are not aware of (Gentile 1998). The two processes reside in different brain areas (Honda et al.

1998), and seem to participate divergently in different skills. For example, verbal instructions which enhance explicit knowledge were found to facilitate the acquisition of some skills (Masters 1992) to have no effect on others (Orrell et al. 2006), and even to degrade the acquisition of yet other skills (Hodges and Franks 2001).

Explicit and implicit processes seem to be involved in sensorimotor adaptation as well. Several studies found that subjects were able to adapt under experimental conditions which left them unaware of the type (Abeele and Bock 2003), or even of the existence of a visual distortion (Bock 1992; Buch et al. 2003). Another study observed that among patients with prefrontal cortical lesions, only those who acquired declarative knowledge of the distortion were also able to adapt (Slachevsky et al. 2003). These findings indicate that sensorimotor adaptation can be achieved either by implicit processes alone or by explicit processes alone, but they leave open whether a joint activation of both processes is beneficial, neutral, or detrimental for adaptation. In a recent study pertinent to this issue (Mazzoni and Krakauer 2006), subjects were exposed to a +45° visual rotation, and were explicitly instructed to point not at the currently highlighted target, but rather at its next neighbor -45° away. Unlike in control subjects, pointing errors of instructed subjects remained low at the onset of exposure, but then gradually increased in an overcompensatory fashion, as if the instructed strategy had algebraically added to "regular" adaptation. This outcome has been interpreted as evidence that adaptation is purely implicit, and cannot benefit from explicit awareness (Mazzoni and Krakauer 2006). Our study was designed to qualify this interpretation. We posit that the particular strategy employed in the above work, deliberate pastpointing, may indeed be detrimental for adaptation, but other explicit processes may be neutral, or even beneficial. To find out, we decided not to prescribe any specific strategy, but rather to assess explicit processes by retrospective self-report.

In literature on sequence learning, explicit processes are often quantified as subjects' declarative knowledge of the stimulus sequence, i.e., subjects are asked to verbally report the sequence in which stimuli had been presented. In analogy, we quantified explicit processes as subjects' declarative knowledge of the visual distortion they were exposed to, and compared the adaptive performance in subjects with and without such knowledge.

2.3 Methods

The experimental set up is outlined in the inset of Figure 1. Subjects observed visual targets through a tilted mirror, such that virtual target positions were in a horizontal plane. They responded by moving their preferred arm in the same plane. The mirror prevented vision of the arm, but the position of their index fingertip was registered by the Fastrak® motion analysis system (resolution 120 Hz, 1 mm), and was displayed to them in real-time as a cursor, along with the targets. In a tracking task, subjects were asked to follow with their finger as accurately as possible a visual target which moved in the display area along an unpredictable path (sum of three sine-waves: 0.31, 0.69, 0.81 Hz for x, 0.13, 0.31, 1.17 Hz for y, phases varying between episodes). Performance was quantified as root mean square tracking error (RMSE), discarding the first 500 ms of tracking to minimize the effects of initial cursor offsets. In a pointing task, subjects had to point as quickly and accurately as possible between a central starting dot and peripheral targets, which appeared at 12 cm distance from the start in one of the eight cardinal and diagonal directions. Targets were presented in a random order. Each appeared for 1.5 s, was then replaced by the starting dot until the finger returned to the center, the next target then appeared, etc. Performance was quantified as error between target and finger direction 100 ms after response onset, i.e., before feedback-based corrections could take effect. In an exploration task, subjects executed discrete point-to-point arm movements in absence of any external targets, while the cursor remained visible as in the other tasks. Subjects were instructed to vary the amplitudes and directions of successive movements as they liked, and were encouraged to explore the whole display area with their hand. Since no targets were presented, no errors could be quantified in this task.

The experiment was subdivided into episodes of 50 s (tracking task) or 30 s duration (pointing and exploration task), which were separated by rest breaks of 5 s duration. Subjects were first familiarized with the experiment by performing one tracking, one pointing, and one exploration episode under normal visual feedback, i.e., the cursor indicated subjects' momentary fingertip position correctly. Data registration then commenced with a baseline phase, which consisted of three tracking and three pointing episodes with normal or absent visual feedback, as shown on the abscissa of Figure 1a. Next came an adaptation phase of 24 episodes, in which visual feedback was rotated by -60° about the starting dot. One half of the subjects executed only the

pointing task during this phase (group P), while the other half executed one pointing episode, then three exploration episodes, then again one pointing and three exploration episodes, etc. (group EP). Figure 1 shows only those episodes in which both groups pointed, since the exploration task could not be quantified. The experiment concluded with the aftereffect phase, which consisted of three pointing episodes without feedback (to assess the persistence of adaptation), two pointing episodes with -60° rotated feedback (to refresh adaptation), and five tracking episodes with -60° rotated feedback (to assess transfer from pointing to tracking).

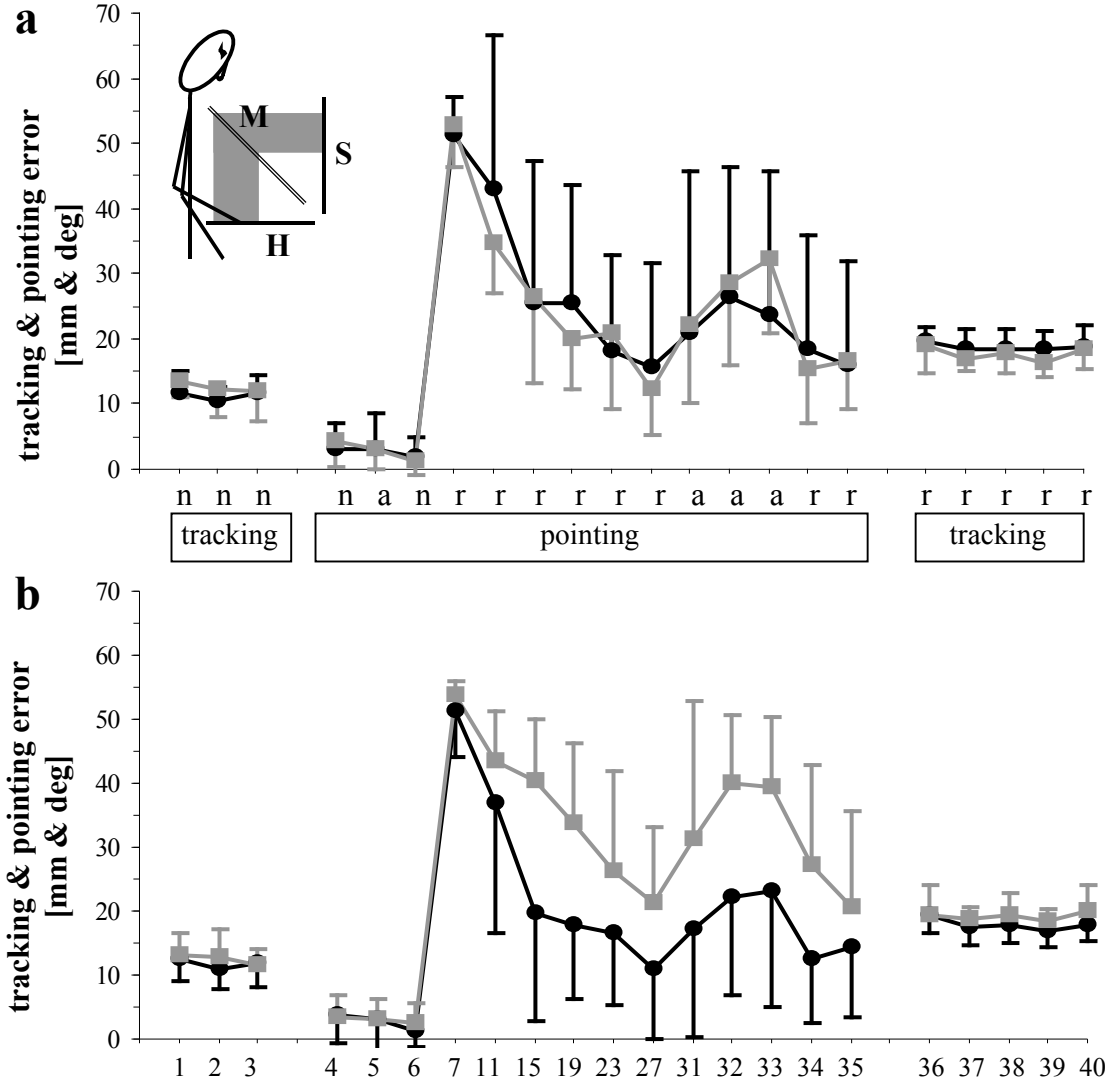

Fig. 1 Inset: Scheme of experimental apparatus with display screen (*S*), mirror (*M*), and horizontal workspace (*H*). **a** Tracking and pointing performance of subjects exposed to a visual rotation while performing the pointing task alone (group *P*, *gray*) or intermixed with the exploration task (group *EP*, *black*). Symbols indicate across-subject means, and *error bars* standard deviations. Abscissa labels indicate normal (*n*), absent (*a*), or 60° rotated (*r*) feedback. **b** Tracking and pointing performance of subjects who correctly described the visual distortion (*black*) and those who didn't (*gray*). Abscissa labels indicate episode numbers.

Before starting, subjects were instructed that the task will "become more difficult" during the experiment, but they will "get used to it". They were not instructed about the nature of this difficulty, nor were they given any advice on how to overcome it. After completion of the experiment, they were asked to write down why, in their opinion, the task had become more difficult. Answers were deemed correct when subjects reported either a rotated visual feedback, or the need for counter-clockwise response corrections. Two subjects apparently misunderstood our question and their responses were therefore discarded.

22 right-handed subjects (10 males, 12 females), aged 20 to 29, participated after signing a written informed consent statement. After discarding the abovementioned two subjects, group P and EP consisted of ten subjects each. None of them exhibited overt sensorimotor deficits besides corrected vision, and none had prior experience in sensorimotor research. The study was part of a research project pre-approved by the authors' institutional Ethics Committee.

2.4 Results

Figure 1a depicts the tracking and pointing performance of group P and EP. Clearly from this presentation, the performance of both groups was very similar throughout all phases of the experiment. Under rotated feedback, pointing errors abruptly increased and then gradually decreased again, as a sign of successful adaptation. When visual feedback was subsequently removed, pointing errors remained relatively low, thus indicating a partial persistence of adaptation. Tracking errors under rotated feedback after adaptation were not much larger than under normal feedback before adaptation, which suggests a successful transfer of knowledge to a new motor task. The similarity of both groups was confirmed statistically. Table 1 shows the outcome of analyses of variance (ANOVA) with the between factor Group and the within-factor Episode, which yielded no significant effects of Group or group × episode on subjects' pointing or tracking errors in the adaptation, persistence, or transfer phase.

To confirm that exploration of the workspace was indeed more complete in the exploration than in the pointing task, we compared several response characteristics of group EP and P in episode 8 and 30 (i.e., in the first and last adaptation episode during which group EP performed the exploration task). Mean movement amplitude in

episode 8 was 144.6 ± 33.1 mm for group EP and 117.7 ± 13.2 mm for group P, which was significantly different ($t(12) = 2.39$; $p < 0.05$). In episode 30, it was 134.6 ± 36.8 mm for group EP and 119.0 ± 5.8 mm for group P, which was no longer significantly different ($t(9) = 1.32$; $p > 0.05$). The within subject standard deviation of movement amplitude in episode 8 was 41.4 ± 24.1 mm for group EP and 17.3 ± 11.9 mm for group P, which was significantly different ($t(13) = 2.83$; $p < 0.05$). In episode 30, it was 31.9 ± 20.3 mm for group EP and 5.9 ± 3.3 mm for group P, which was also significantly different ($t(9) = 4.00$; $p < 0.01$). The dispersion of movement starting points[2] in episode 8 was 13,231 ± 12,619 mm^2 for group EP and 65 ± 38 mm^2 for group P, which was significantly different ($t(9) = 3.29$; $p < 0.01$). In episode 30, it was 7,879 ± 9342 mm^2 for group EP and 50 ± 35 mm^2 for group P, which was again significantly different ($t(9) = 2.65$; $p < 0.05$). Thus summing up, starting points and movement amplitudes varied substantially more in the exploration than in the pointing task, which suggests that subjects visited a larger portion of the workspace in the former than in the latter task.

	Group			Episode			Group × episode		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
Adaptation	1,18	0.15	>0.05	**3,57**	**41.57**	**<0.001**	3,57	1.04	>0.05
Persistence	1,18	0.27	>0.05	**2,36**	**4.78**	**<0.05**	2,36	1.56	>0.05
Transfer	1,18	1.25	>0.05	3,50	2.81	>0.05	3,50	0.66	>0.05

Tab. 1 Outcome of analyses of variance using the between-factor group and the within-factor episode, when applied to the tracking and pointing errors of the adaptation, persistence, and transfer phase. Statistical significance is highlighted in bold.

Subjects' verbal retrospective reports regarding task difficulty, and our classifications of those reports, are presented in Table 2. Thus, seven of the ten subjects from group P described the distortion correctly, as did seven of the ten subjects from group EP. We therefore have no evidence that one of the two adaptation regimes is more beneficial for declarative knowledge than the other.

[2] This characteristic was defined by calculating the standard deviation of starting point along the *x* and *y* axis, *sx* and *sy*, and then calculating the area of an ellipse with those standard deviations as half-axes, i.e., $\pi * sy * sy$.

Figure 1b illustrates the tracking and pointing performance of our subjects when sorted by the presence or absence of declarative knowledge, rather than by group. Clearly, subjects with declarative knowledge exhibited a more pronounced adaptation, a better persistence, but no better transfer than the remaining subjects. These observations are confirmed by an ANOVA with the between-factor knowledge and the within-factor episode shown in Table 3, as significant effects of knowledge for adaptation and retention, but not for transfer.

Subject	Response	Classification
s1	Displaced 45° clockwise	Correct
s2	Rotated 40° to the left	Correct
s3	Displaced 45° to the right	Correct
s4	Always 45° counterclockwise	Correct
s5	Deflection of 45°	Correct
s6	Displaced 30° to the left	Correct
s7	Displacement about a certain angle (45° or more)	Correct
s8	Rotated about always the same angle	Correct
s9	Drifted to the left side	Correct
s10	Always slight flection	Correct
s11	Always had to point approximately 30° aside in a circle	Correct
s12	Cursor had strong angular momentum to the left	Correct
s13	Always changed about a certain angle (45°)	Correct
s14	Tracing in a different angle	Correct
s15	Cursor and movement of the hand do not correspond	Incorrect
s16	Diagonal = across, diagonal = straight up, vertical = diagonal,...	Incorrect
s17	Finger from right to left = cursor above right to down left, ...	Incorrect
s18	Straight movements with index finger no longer possible	Incorrect
s19	Cursor and movement of the hand do not correspond	Incorrect
s20	Cursor and movement of the hand do not correspond	Incorrect

Tab. 2 Subjects' verbal reports, and their classification. The reports were translated from German to English for the purposes of this publication.

It is conceivable that subjects without declarative knowledge, who produced larger pointing errors during the adaptation and persistence phase, compensated for those errors by making larger corrections near the end of movement. To find out, we determined the pointing error not only 100 ms after movement onset but also at movement end, and used the difference between both as a measure of response corrections. The ANOVA in Table 4 yielded no significant effects of knowledge or knowledge × episode on response corrections; the effect of Episode reflects the decrease of corrections from about 35° at adaptation onset to about 15° at adaptation end. We therefore found no evidence for the above view, that subjects without declarative knowledge made larger corrections.

	Group			Episode			Knowledge×episode		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
Adaptation	**1,18**	**5.42**	**<0.05**	**3,55**	**32.75**	**<0.001**	3,55	1.89	>0.05
Persistence	**1,18**	**4.74**	**<0.05**	**2,36**	**4.47**	**<0.05**	2,36	0.25	>0.05
Transfer	1,18	1.43	>0.05	4,72	1.92	>0.05	4,72	0.61	>0.05

Tab. 3 Outcome of analyses of variance using the between-factor declarative knowledge and the within-factor episode, when applied to the tracking and pointing errors of the adaptation, persistence, and transfer phase. Statistical significance is highlighted in bold.

	Group			Episode			Knowledge×episode		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
Adaptation	1,18	2.00	>0.05	**3,49**	**7.98**	**<0.001**	3,49	1.45	>0.05
Persistence	1,18	0.00	>0.05	2,36	1.16	>0.05	2,36	0.15	>0.05

Tab. 4 Outcome of analyses of variance using the between-factor declarative knowledge and the within-factor episode, when applied to the error corrections of the adaptation and persistence phase. Statistical significance is highlighted in bold.

2.5 Discussion

One purpose of our study was to determine whether sensorimotor adaptation is enhanced when subjects are not limited to a set of eight movements, but rather can free-

freely explore the distorted workspace to any desirable detail. Since the transfer of adaptation to unpracticed locations is already perfect with eight targets (Krakauer et al. 2000), we didn't expect a further improvement of unconstrained exploration, and therefore didn't test for this type of transfer. Instead, we tested for the time-course of adaptive improvement, the persistence of adaptation when visual feedback is withheld, and the transfer of adaptation from pointing to tracking movements. Our data provide no evidence for a benefit of unconstrained exploration on any of those phenomena, which is in accordance with the view that practice with eight equal-amplitude movements is already variable enough to support global adaptation. This outcome is relevant for the interpretation of earlier work. Most previous adaptation studies used an eight-target task similar to the present work, but some opted for different pointing regimes, in order to sample a larger portion of the workspace (Flanagan et al. 1999; Graydon et al. 2005). The present data support the view that all above studies dealt with the same adaptive mechanisms, in spite of their methodological differences.

The second purpose of our study was to evaluate the role of declarative knowledge for adaptation. We found that subjects who correctly described the nature of our distortion also showed a more pronounced adaptive improvement and a stronger persistence, but not an enhanced transfer of adaptation to a new motor task. This pattern of findings suggests that the benefits of declarative knowledge are short-lived and/or situation-specific, two characteristics previously attributed to the strategic control (Redding and Wallace 1996; McNay and Willingham 1998; Bock 2005): In short, it is thought that adaptive improvement is achieved by two processes, a recalibration of sensory-to-motor transformation rules, and strategic adjustments which include feedback-based corrections and various cognitive workarounds. We therefore conclude that subjects with declarative knowledge improved their adaptive progress by a more intensive use of strategic adjustments. Among the various strategies discussed in literature, feedback-based corrections can probably not explain our data, since corrections were excluded by our analysis procedure (see Methods). Likewise, deliberate pastpointing can be discounted since it is detrimental rather than beneficial for adaptation (Krakauer et al. 2000). More likely alternatives are the associative learning of stimulus-response pairs, anticipatory response adjustments for errors experi-

enced on previous trials, cognitive updating of perceived feedback positions (Redding 1996), as well as real or virtual changes of body posture (Redding et al. 2005).

Summing up, our findings suggest that subjects with declarative knowledge about the distortion augmented their adaptive progress through strategic adjustments. However, the causal relationship between knowledge and strategies still needs to be explored: we believe that declarative knowledge invoked accordant strategies, but our data are also compatible with the view that the use of strategies invoked declarative knowledge.

2.6 Acknowledgements

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3 Second study:
Mechanisms for visuomotor adaptation to left-right reversed vision

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Reference

Werner S, Bock O (2010) Mechanism for visuomotor adaptation to left-right reversed vision. Hum Movement Sci 29: 172-178

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3.1 Abstract

Behavioral studies suggest that the adaptation of planar arm movements to rotated visual feedback is achieved by the interplay of a gradual process which slowly rotates subjects' responses by up to +/-90°, and a discrete process which changes the responses by means of axis inversion. The processes for adaptation to left-right reversed visual feedback are far less well understood. To clarify this issue, 12 healthy subjects performed pointing movements to targets presented in eight different directions, before and during exposure to left-right reversed visual feedback. We quantified the direction of each response 150 ms after movement onset and analyzed the time-course of those directions throughout the adaptation phase, separately for different targets. For targets along the axis of inversion, we only found an increase of response variability, for targets perpendicular to that axis, we observed a discrete 180° change of response direction, and for diagonal targets, we found a discrete 180° change followed by a gradual "backward" shift of 90°. The present findings confirm that sensorimotor adaptation is based on discrete and gradual processes, that both types of processes can occur concurrently, and suggests that those processes can contribute to adaptation in a target-specific fashion.

3.2 Introduction

The human sensorimotor system can adapt to a variety of visual distortions such as lateral shifts, magnifications, mirror-reversals, and rotations of the visual input. The latter type of distortion has been particularly well investigated. Adaptation to rotations up to 90° is achieved by a continuous process which gradually changes subjects' responses up to the required angle of rotation; adaptation to larger angles therefore takes longer (Cunningham 1989; Imamizu and Shimojo 1995; Abeele and Bock 2001a; Ferrel et al. 2001), but benefits from a pre-adaptation to smaller angles (Abeele and Bock 2001b; Wigmore et al. 2002). In contrast, adaptation to a 180° rotation is quick and discrete (Cunningham 1989; Imamizu and Shimojo 1995; Abeele and Bock 2001a; Ferrel et al. 2001), as it is probably achieved at fairly low cost by an axis inversion (Cunningham 1989). Finally, adaptation to rotations between 90° and 180° is achieved by a combination of both above processes, i.e., a quick 180° change followed by a gradual "backward" rotation towards the required angle (Bock et al. 2003).

Unlike adaptation to visual rotations, adaptation to reversed vision has been less well studied in the past. At a first glance, it might seem obvious that it is at least as fast as adaptation to 180° rotations, since it can be achieved by inverting just one rather than two axes. However, experimental evidence does not support such a view: adaptation to reversals is actually quite slow (Miyauchi et al. 2004; Caselli et al. 2006), with movement errors about as high as under 90° rotations (Cunningham 1989). Detailed analyses yielded that targets presented along the axis of reversal – which required no adaptive change – yielded higher errors than targets presented perpendicular to that axis (Cunningham and Pavel 1991), that the incidence of correctly aimed movements increased during adaptation from 60% only to 75%, and that incorrect movements were typically aimed as in novice subjects rather than in other directions (Caselli et al. 2006). These findings illustrate the complexity of adaptation to visual reversals, but they do not reveal the principles by which this adaptation is achieved.

While adaptation to visual reversals seem to be as slow as that to 90° rotations, it is difficult to envisage that it acts gradually as well: an internal representation of space can gradually rotate from 0° through intermediate angles up to 90°, but how can it gradually invert one of its axes? Here we present evidence that adaptation to visual

reversals is achieved by a combination of gradual and discrete processes, much like those involved in adaptation to visual rotations.

3.3 Methods

The experimental apparatus is shown schematically in Figure 1A. Subjects pointed at mirror-viewed visual targets which appeared in a horizontal plane. The position of their index fingertip was registered by the Fastrak® motion analysis system with a sampling frequency of 120 Hz and a resolution of 1 mm. The registered signal was used to display a cursor along with the targets, hence subjects received visual feedback about their finger position without actually seeing their arm. We instructed the subjects to point as accurately and quickly as possible from a central starting dot to peripheral targets and back again (Figure 1B). The targets were presented in random sequence, at eight possible positions along an imaginary circle of 100 mm radius; each stayed on for 700 ms, and was then replaced by the starting dot until the cursor returned to the centre.

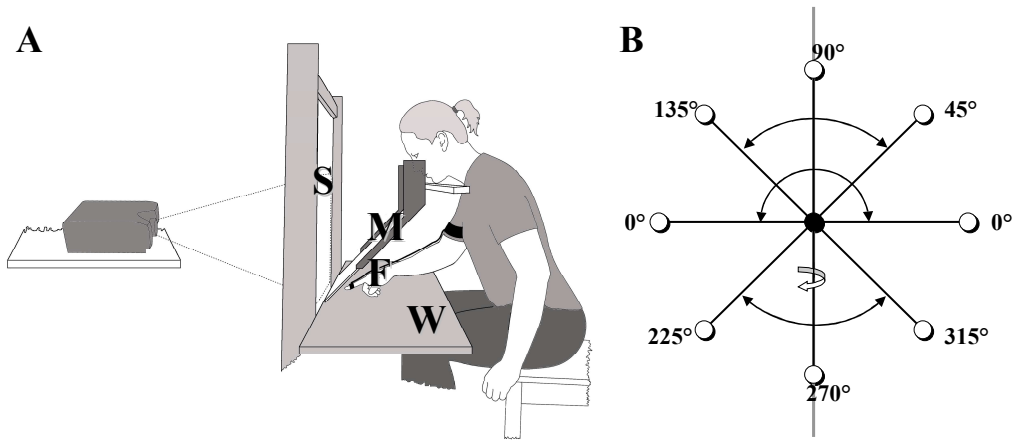

Fig. 1 A Scheme of experimental apparatus with display screen (S), mirror (M), working plane (W), and Fastrak® sensor (F). **B** Layout of targets and central starting dot. Arrows indicate the effect of left-right reversed feedback; e.g., when subjects move their finger towards the 45° target, they see it moving towards the 135° target.

The experiment was subdivided into episodes of 30 s duration, separated by rest breaks of 5 s duration. First, subjects were familiarized with the experiment in two episodes under veridical visual feedback. Data collection then started with three *baseline* episodes, again under veridical feedback, followed by 40 *adaptation* epi-

sodes under left-right reversed feedback. We quantified subjects' pointing performance as finger direction with respect to the target 150 ms after movement onset, i.e., before feedback-based corrections could become effective. While it is customary to summarize subjects' performance as the mean direction and its standard deviation for a each episode, we decided instead to depict the *distribution of directions* for each episode, to emphasize the fact that many of those distributions were bimodal. Separate distributions were derived for responses to targets at 90° and 270°, which required no adaptive change, to targets at 0° and 180°, which required a reversal of direction, and for the remaining, diagonal targets, which required a change of +90° or –90° (see Figure 2).

Twelve healthy right-handed subjects (age 24.58 ± 4.38 years; 4 female, 8 male) participated. None had previous experience in sensorimotor research. The authors' local Ethics Committee had approved the procedure of the experiment, and all subjects gave written informed consent.

3.4 Results

Original registrations of finger paths produced by one subject at the onset of adaptation are shown in Figure 2. Targets at 90° and 270° required no adaptive change, and accordingly, most finger paths are aimed directly at those targets; however, one response is inadequately aimed in the opposite direction (Figure 2A). Targets at 0° and 180° required a reversal of movement direction, and indeed, several early-adaptation responses already show reversals (Figure 2B). Diagonal targets required a +90° or -90° response change, but the finger paths are actually aimed either towards or opposite to the targets (Figure 2C).

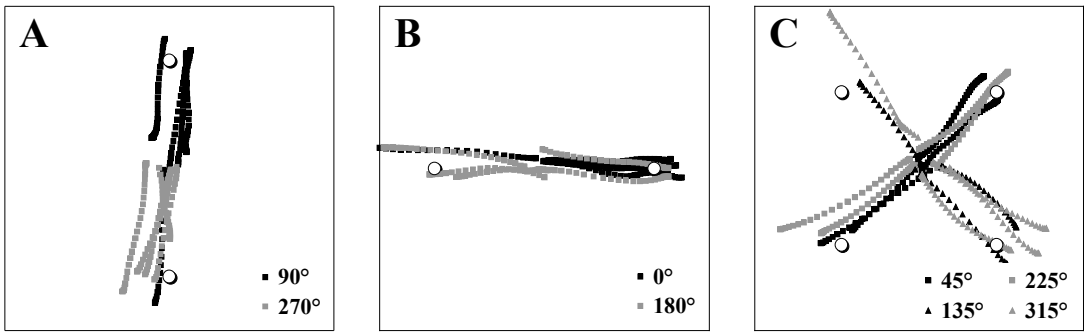

Fig. 2 Movement paths of one subject at the onset of adaptation to targets at 90° and 270° (**A**), 0° and 180° (**B**), and all diagonal targets (**C**).

Figure 3 illustrates the distribution of all response directions from the same subject, in the different adaptation episodes. Figure 3A depicts responses to targets at 90° and 270°, Figure 3B to those at 0° and 180°, and Figure 3C to the diagonal targets; to accommodate all diagonal targets in a single plot, we inverted the sign of responses to targets requiring a +90° rather than a -90° change. Already a look at these single-case data suggests that the time-course of adaptation might differ between the three target groups depicted in Figure 3A-C, respectively.

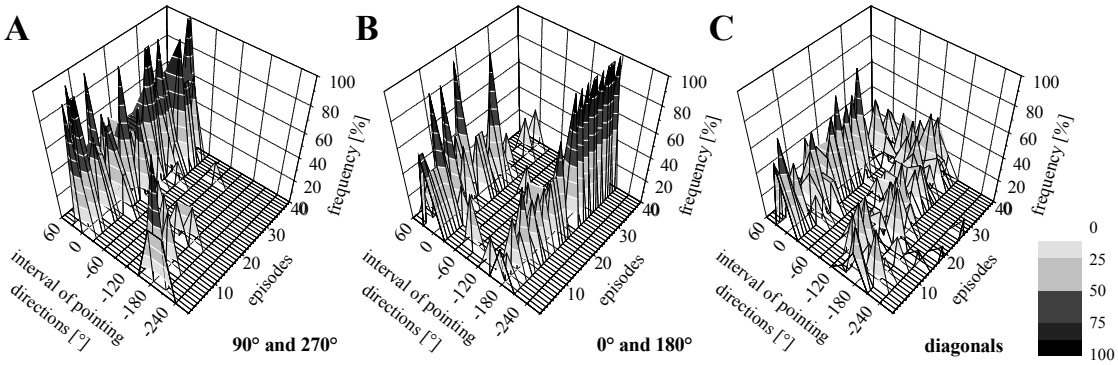

Fig. 3 Distribution of movement directions for the same subject as in Fig. 2. The 360° range of possible directions was subdivided into 30° bins centered about 0°. Bin width *h* was estimated with the rule of Freedman–Diaconis with $h = \frac{2 \times IQR(x)}{\sqrt[3]{n}}$, where *IQR(x)* is the interquartile range and *n* the number of movements within each episode. The frequency of movements (z-axis & grayscale) for each bin (y-axis) is shown separately for each adaptation episode (x-axis). As in Fig. 2, data are plotted separately for targets at 90° and 270° (**A**), 0° and 180° (**B**), and diagonal targets (**C**).

Figure 4 shows the distributions of response directions across all subjects. In contrast to Figure 3, we decided for a two-dimensional grayscale representation which might be less intuitive, but which prevents smaller ridges to "hide" behind larger ones. Arrows were added in Figure 4 to indicate pointing directions which correspond to complete adaptation.

As shown in Figure 4A, responses to targets at 90° and 270° remained centered around the target direction. Only a minority of responses early during adaptation were aimed opposite to the targets. Variability was larger during adaptation than during baseline: the standard deviation of all baseline episodes (8.03°) differed significantly from that of the first five adaptation episodes (40.87°): $t(1,12) = -3.274$; $p < 0.01$. From Figure 4B, responses to targets at 0° and 180° were distinctly bimodal, with one peak aligned with the target direction and the other peak with the opposite direction, representing fully adapted behavior. The former peak became gradually

lower, and the latter became gradually higher during the adaptation phase, but their directional alignment remained steady. Figure 4C illustrates that responses to diagonal targets were bimodal as well. One peak was again aligned with target direction. The other peak was initially aligned with the opposite direction, but gradually shifted throughout the adaptation phase towards the value of -90° required for complete adaptation. Again, the peak aligned with the target direction became gradually lower, while the other peak became gradually higher during the adaptation phase.

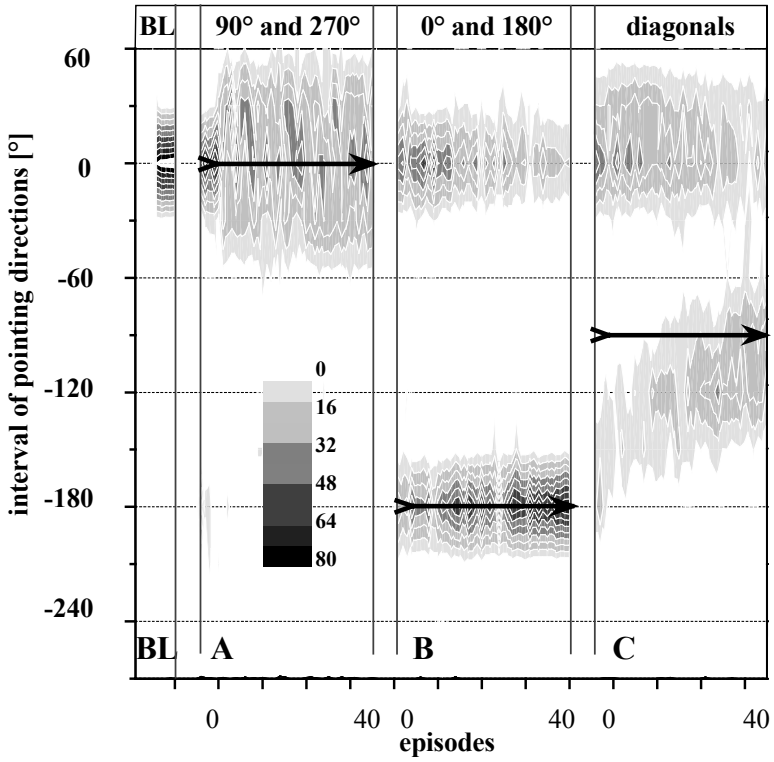

Fig. 4 Distribution of movement directions for all subjects. Across-subject means were calculated in the same way as the individual-subject data in Fig. 3, and plotted as 2D graphs with grayscale coding of frequency. Bins representing full adaptation are marked by arrows. As in Fig. 2 and 3, graph **A** shows the results for targets at 90° and 270°, **B** for 0° and 180°, **C** for all diagonal targets; additionally, BL shows baseline data.

To compare the extent of adaptation for the different targets, we calculated the percentage of responses that were aimed within ±15°, around the direction of full adaptation during the last three adaptation episodes. This ±15° interval corresponds to the intervals of pointing directions we had estimated for the distributions of response directions (Figures 3 and 4). The mean percentage ± standard deviation across subjects was 36.81% ± 29.76% for targets at 90° and 270°, 71.57% ± 30.08% for targets at 0° and 180°, and 27.36% ± 21.93% for diagonal targets. The difference between

target groups was significant in a one-way analysis of variance ($F(2,33) = 8.591$; $p < 0.001$), with Fisher's LSD post-hoc tests revealing that only the 0° and 180° targets differed from the other target groups. Thus, by the end of adaptation, the percentage of correctly aimed responses was smaller for targets at 90° and 270° which required no adaptive change, than for targets at 0° and 180° which did require adaptive change.

Figure 5 illustrates the efficiency of adaptation across all targets which required an adaptive change (i.e., excluding targets at 90° and 270°). During the first adaptation episode, the majority of responses were aimed within ±15° around the target direction, and thus were not adapted; only few responses were aimed within ±15° around the direction representing full adaptation. During the last three adaptation episodes, this relationship was reversed. This observation was supported by an analysis of variance with the within-factors Episode (first, last three), and Response direction (naive, adapted), which yielded a significant interaction of Episode × Response direction ($F(1,11) = 12.679$; $p < 0.01$).

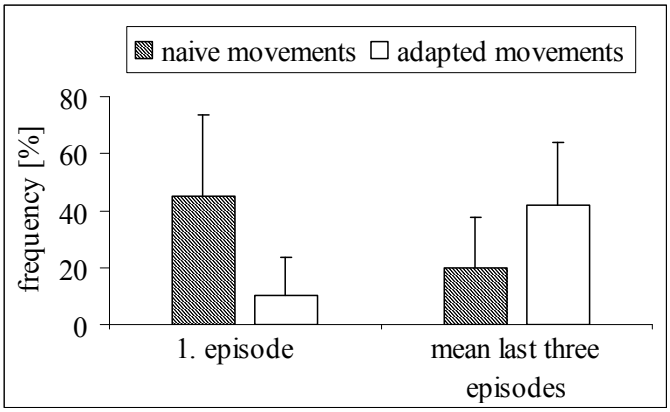

Fig. 5 Streaked bars indicate the frequency of unadapted response directions (bin centered around 0°), and white bars the frequency of fully adapted response directions (bin centered around +/-90° or 180°, depending on target). To the left are across-subject means from the first, and to the right those from the last three adaptation episodes.

3.5 Discussion

The aim of the present study was to evaluate the principles of adaptation to visual left-right reversal. Previous work has shown that adaptation to a 180° rotation can be achieved very fast, probably by inverting both spatial axes (Cunningham 1989; Bock et al. 2003). On might therefore expect that adaptation to a left-right reversal is at least equally fast, since only one axis needs to be inverted. However, previous au-

thors reported that adaptation to this distortion is slow (Cunningham 1989; Miyauchi et al. 2004; Caselli et al. 2006), and our own data confirm this observation: after 20 minutes, or about 480 trials, only 42% of responses were fully adapted, and 20% resisted any change. The inversion of a single axis therefore seems not to be a readily available adaptive process. In line with the findings of Cunningham and Pavel (1991), we also showed that movements along the axis of reflection produce higher errors than movements along the axis perpendicular to it.

The main outcome of the present study is that adaptive changes took a different course for different targets. For targets on the axis of reversal, response direction became more variable but did not change systematically. For targets perpendicular to that axis, responses were aimed either at the target or opposite to it, with prevalence gradually shifting from the former to the latter. For targets on the diagonals, responses were aimed either at the target or in a direction which was initially opposite, and then gradually changed towards -90°; again, prevalence gradually shifted from the former to the latter. The findings for diagonal targets are quite reminiscent of our previous data on adaptation to large visual rotations: there as well, responses were initially aimed opposite to the targets and then gradually shifted until they became adequate for the imposed rotation (Bock et al. 2003). It therefore seems conceivable that the same interplay of a discrete 180° switch and a gradual change of direction may be invoked by both visual distortions. In this sense, our data confirm the existence of a discrete and a gradual adaptive process. Moreover, the present findings document for the first time that these processes can be activated simultaneously and in a target-specific fashion: both the discrete and the gradual process for some targets, only the discrete process for other targets, and none of them for yet other targets.

The target-specific adaptive changes observed in the present study could be interpreted as evidence that adaptation is organized in multiple functional modules, each pertinent to a narrow range of response directions. Such a view is in accordance with the finding that adaptation to rotated vision can be direction-specific (Krakauer et al. 2000; Woolley et al. 2007) just as it can be specific for an endeffector (Bock et al. 2005), target colour (Wada et al. 2003; Mistry and Contreras-Vidal 2004; Osu et al. 2004), or head orientation (Seidler et al. 2001). But it is in conflict with the observation that adaptive changes of the visuomotor gain imperatively generalize across di-

rections (Krakauer et al., 2000; Bock, 1992) except when visual feedback is terminal (Heuer & Hegele, 2008; Hegele & Heuer, 2010). As further evidence against independent, direction-specific modules, we observed several signs of interference between directions. First, response variability increased for targets at 90° and 270°, although these targets required no adaptive changes whatsoever. Second, the incidence of responses directed opposite to targets at 0° and 180° developed slowly over time, and not abruptly as in experiments on adaptation to rotated visual feedback (Bock et al. 2003). Third, responses to the opposite direction, e.g., a 180° inversion, could be observed for all target directions.

In conclusion, our data indicate that adaptation to reversed vision can be based on the same discrete and continuous processes as adaptation to rotated vision, and that those processes can operate simultaneously and in a target-specific fashion. Further work is needed to determine whether those processes change a global internal representation of space, or rather multiple direction-specific modules.

3.6 Acknowledgements

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4 Third study:
Adaptation to mirror-reversed vision is based on directionally tuned modules

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Reference

Werner S, Bock O (revision) Adaptation to mirror-reversed vision is based on directionally tuned modules. Hum Movement Sci
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4.1 Abstract

Sensorimotor adaptation to rotated visual feedback is thought to be achieved by directionally tuned modules. Here we scrutinize whether adaptation to reversed vision utilizes similar mechanisms. Specifically, we hypothesize that adaptive transfer to unpracticed target directions is determined by the superposition of neighboring modules. One group of subjects adapted to a left-right reversal of visual feedback, which requires a 180°, ±90°, or no change of response direction, depending on target position. Two groups of control subjects adapted to a 180° and to a 90° rotation of visual feedback. We found that adaptation to a left-right reversal is less efficient than adaptation to rotations requiring the same adaptive change, and attribute this decrement to interference between neighboring modules. We further found that transfer to unpracticed targets is well predicted by a simple Gaussian model. From this we conclude that adaptation to a left-right reversal emerges in a regional and interdependent fashion, and can be modeled as overlapping Gaussian tuned processes.

4.2 Introduction

Sensorimotor adaptation to rotated visual feedback is based on two distinct mechanisms. Rotations up to 90° are compensated by a gradual rotation of an internal reference frame, from its original orientation through intermediate angles up to the required angle. Rotations of 180° are compensated by a discrete inversion of the x and y axes, and rotations between 90 and 180° by a combination of both, i.e., axes inversion followed by gradual "backward" rotation (Bock et al. 2003). We have recently reported that adaptation to mirror-reversed visual feedback utilizes similar mechanisms, and engages them in a target-specific fashion. Thus, responses to targets along the axis of reversal remain largely unchanged throughout the adaptation process, those to targets orthogonal to that axis are characterized by a discrete inversion, and those to targets in diagonal directions by a gradual rotation up to +90 or -90°, as adequate (Werner and Bock 2010). These adaptive changes proceed concurrently, as if adaptation is based on multiple independent, target-specific modules.

The notion of target-specific adaptive modules is supported by studies on the transfer of adaptation to unpracticed targets. Subjects exposed to *magnified* visual feedback showed good transfer to new target distances and directions (Bock 1992; Krakauer et al. 2000), which suggests that gain adaptation is a global process. In contrast, subjects exposed to *rotated* feedback showed good transfer only to new distances (Krakauer et al. 2000), while transfer to new directions gradually decreased with increasing angular difference from the trained direction (Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Pine et al. 1996; Krakauer et al. 2000; Wang and Sainburg 2005). This suggests that adaptation to rotated feedback is based on modules which are directionally tuned, possibly in a Gaussian manner (Ghahramani et al. 1996; Tanaka et al. 2009). The existence of such directionally tuned modules could also explain that subjects can concurrently adapt to multiple visual rotations when each is presented in a different workspace region (Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Krakauer et al. 2000).

If adaptation to mirror-reversals indeed utilizes similar mechanisms as adaptation to rotations, it should also be governed by directionally tuned modules. The present study was designed to scrutinize this prediction. Specifically, we hypothesized that the transfer to unpracticed target directions is determined by the superposition of

neighboring adapted modules. To find out, we compared experimental data of the transfer of adaptation to mirror-reversed vision with predictions of a simple Gaussian model.

4.3 Methods

Experimental Set-up

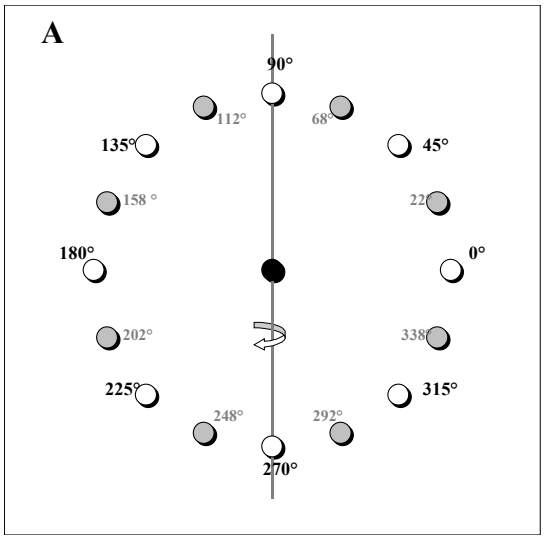
We used the same experimental apparatus as in our preceding study (Werner and Bock 2010). In short, subjects performed center-out-and-back pointing movements to eight randomly lit targets without vision of their hand. Fingertip position was recorded with a sampling frequency of 120 Hz and a spatial resolution of 1mm, and displayed to the subjects as a cursor along with the targets.

Participants and Procedure

Forty-eight right-handed subjects participated (25.6 ± 2.8 years of age; 19 female, 29 male). All were healthy with normal or corrected-to-normal vision, had no prior experience in sensorimotor research, and signed an informed consent statement before the experiment. The study was part of a research project pre-approved by the authors' local Ethics Committee.

Subjects were asked to point at each target as accurately and quickly as possible during episodes of 30 s duration, separated by 5 s rest breaks. In a given episode, targets were presented either in the eight cardinal and diagonal directions (target set A, white dots in Figure 1A), or in the eight interposed directions (target set B, gray dots in Figure 1A)[3]. Cursor feedback was veridical during the initial five episodes of the experiment (two familiarization and three baseline episodes), and was then distorted either by left-right reversal, by 90° rotation or by 180° rotation. Target sets and distortions varied between subject groups as per Figure 1B. Note from this presentation that subjects from group LRR adapted with target set A, and were tested with target set B once in the middle of adaptation (transfer phase I) and once at its end (transfer phase II).

[3] Due to technical reasons only whole-numbered target directions could be chosen. Therefore transfer targets were located at 22° instead of 22.5°, 68° instead of 67.5° and so on.



B	# of episodes	distortion	target set
LRR	23	left-right reversal	A
	2	left-right reversal	B
	23	left-right reversal	A
	2	left-right reversal	B
LRR-ctr	1	left-right reversal	B
ROT-90	40	90° rotation	A
ROT-180	40	180° rotation	A

Fig. 1 A Target display, showing the central starting dot, target set A (*white dots*) and target set B (*gray dots*). **B** Order of distortions and target sets for each experimental group.

Data Processing

Subjects' pointing direction was determined as the difference between hand and target direction 150 ms after response onset, that is, before feedback-based corrections became effective. Thus, complete adaptation to +90° rotated feedback would correspond to a change of pointing direction from 0° to -90°. As in our previous study (Werner and Bock 2010), we calculated the percentage of well-adapted responses *PA* based on those responses which deviated by less than ±15° from complete adaptation. This was done separately for each target direction, episode and group. The outcome was submitted to analyses of variances (ANOVAs) with the within-factor Episode and the between-factor Group. Huynh-Feldt-corrections were applied when necessary to compensate for heterogeneity of variances. Significant effects were explored with Fisher LSD post-hoc tests.

We further calculated the frequency distributions of response directions separately for each episode across all targets (group ROT-90 and ROT-180), or separately for targets requiring no adaptive change, those requiring 180° rotation, and those requiring ±90° rotation (groups LRR and LRR-ctr). For targets requiring a +90° change, we inverted the sign of pointing directions before combining them with those to targets requiring a -90° change. A more detailed description of this procedure is presented elsewhere (Werner and Bock 2010)(Werner and Bock 2010).

If transfer to an untrained target direction θ reflects the superposition of Gaussian tuning curves (see Introduction), the following should hold:

$$PA(\theta) = \sum_{i=0}^{8} a_i \exp(-\frac{(\theta - 45*i)^2}{2\sigma^2}) . \quad (1)$$

Here, σ is the tuning width and a_i is the peak value of the tuning curve for trained direction *i**45°. We compared the values predicted by Eq. (1) with the data actually collected in the first episode of transfer I and II.

4.4 Results

Time course of adaptation

The filled symbols in Figure 2 depict the percentage of well-adapted responses during the first 40 adaptation episodes of group LRR, separately for targets requiring no change (Figure 2A), a 180° change (Figure 2B), and a 90° change (Figure 2C). These data are compared to the *PA* scores for the same targets under conditions when all targets were associated with the same distortion (open symbols). Two-way ANOVA yielded a significant effect of Episode for the scores in Figure 2B ($F(23.32,512.99) = 4.262$; $p < 0.001$) as well as 2C ($F(7.80,148.28) = 17.385$; $p < 0.001$); the effects of

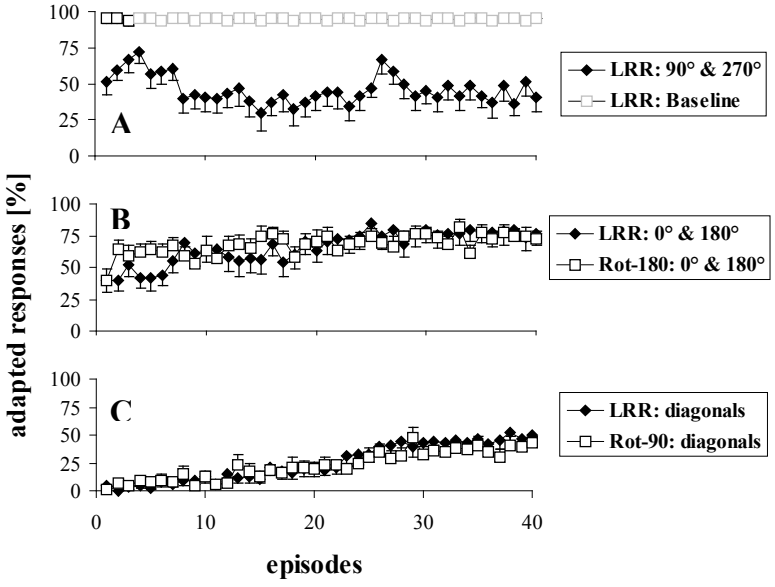


Fig. 2 Mean *PA* ± standard errors across subjects of the first 40 episodes in each group, comparing responses to the same targets requiring the same adaptive change under different experimental conditions. **A** Responses to 90° and 270° targets during adaptation and during the baseline of LRR. **B** Responses to 0° and 180° targets during adaptation of LRR and ROT-180. **C** Responses to diagonal targets during adaptation of LRR and ROT-90.

Group and Episode × Group were not significant for either data set. It was not possible to apply two-way ANOVA to the scores in Figure 2A, since the comparison data consist of three episodes only (i.e., baseline episodes of group LRR). We therefore took another approach: for each subject, we calculated the difference between each adaptation episode and the mean of the three comparison episodes, and submitted the outcome to a one-way ANOVA with the factor Episode. The constant term was significant ($F(1,11) = 50.390$; $p < 0.001$), indicating that the percentage of well-adapted responses was reliably lower in the adaptation than in the comparison data.

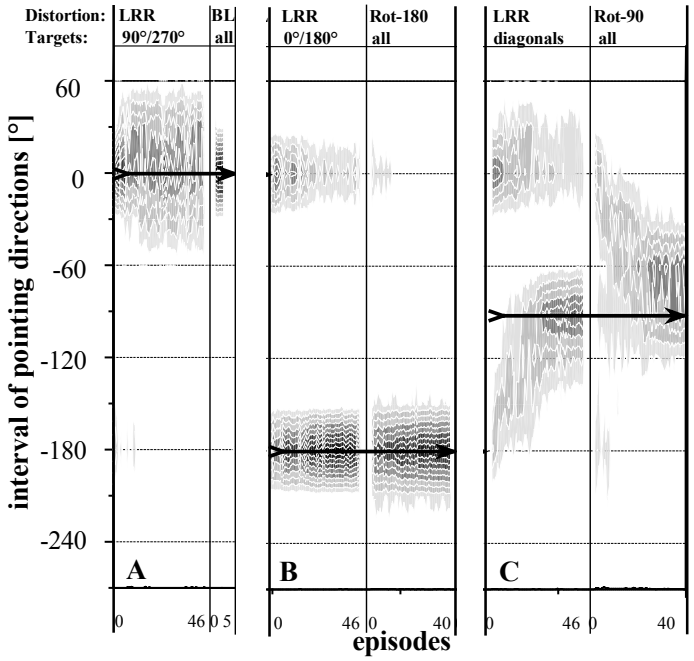


Fig. 3 Frequency distribution of the same data as in Fig. 2 in a grayscale plot. The 360° range of possible directions was subdivided into 30° bins centered about 0°. Estimation of bin width h was implemented with the Freedman-Diaconis rule with $h = \frac{2 \times IQR(x)}{\sqrt[3]{n}}$, where n is the number of movements within each episode and IQR(x) the interquartile range. The across subject means of the frequency of movements (*grayscale*) for each bin (*y-axis*) is shown separately for each adaptation episode (*x-axis*).

Figure 3 illustrates the actual distributions of the response directions summarized in Figure 2. According to Figure 3A, the difference between adaptation and comparison scores observed in Figure 2A was due to higher response variability rather than to a systematic bias, and to a few responses early during adaptation which were aimed opposite to the targets. Figure 3B confirms that adaptation to a 180° rotation is achieved by gradually increasing the incidence of adapted responses at the expense of non-adapted responses rather than by a gradual change of response direction

(Bock et al. 2003), and illustrates that this increase is more pronounced in group ROT-180 than in group LRR, where naïve responses still appeared at the end of adaptation. Finally, Figure 3C shows that adaptation to a 90° rotation was achieved by a gradual change in group ROT-90, but by a maladaptive switch of 180° followed by a gradual "backward" change towards -90° in group LRR; some naïve responses were retained in the latter group even by the end of the adaptation phase. Thus summing up, the distribution of response directions throughout adaptation of group LRR differed from that of comparison data, and this difference was observed for all target directions.

This observation was confirmed by an exemplary analysis of the 20th adaptation episode. Figure 4 shows the distributions of response directions in group LRR and in the comparison data, again separately for targets requiring no change (Figure 4A), a 180° rotation (Figure 4B), and a 90° rotation (Figure 4C). An ANOVA with the within-factor Direction interval and the between-factor Group was applied to intervals with non-zero scores, and yielded a significant Interaction for the data in Figure 4A ($F(2.20,48.39) = 51.945$; $p < 0.001$), 4B ($F(1.30,28.54) = 59.174$; $p < 0.05$) and 4C ($F(5.31,116.87) = 4.294$; $p < 0.01$).

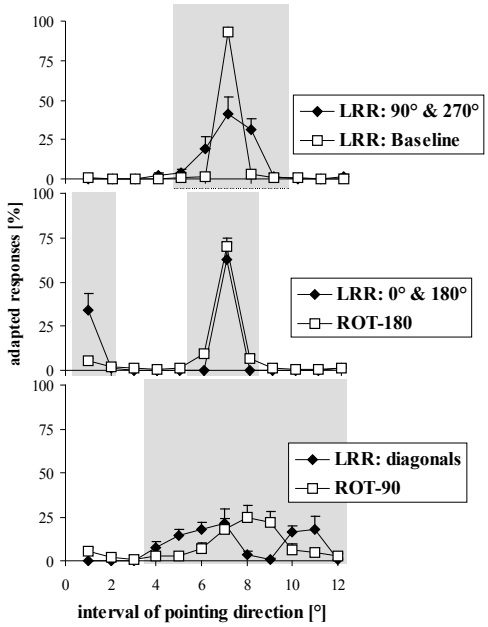


Fig. 4 Mean frequency distribution of response directions ± standard errors across subjects in episode 20 for the same targets and conditions as in Fig. 2. Intervals of pointing directions that were used for an ANOVA are highlighted in gray.

Transfer to untrained target directions

Figure 5 compares the *PA* scores at the onset of the first and second transfer phase of group LRR with those at the onset of adaptation in group LRR-ctr, collapsed across target directions. Note that during those episodes, both groups pointed at target set B under left-right reversed vision, but group LRR-ctr was naïve while group LRR was pre-adapted with target set A. The illustration shows that *PA* was larger in LRR than in LRR-ctr during the first transfer episode, and even more so during the second transfer episode. Accordingly, one-way ANOVA with the within-factor transfer Phase (I, II), applied to the differences between each LRR subjects' scores and the mean LRR-ctr score, yielded a significant constant ($F(1,11) = 11.775$; $p < 0.01$) and a significant effect of Phase ($F(1,11) = 10.301$; $p < 0.01$). Thus, the observed difference between groups and between transfer phases could be confirmed statistically.

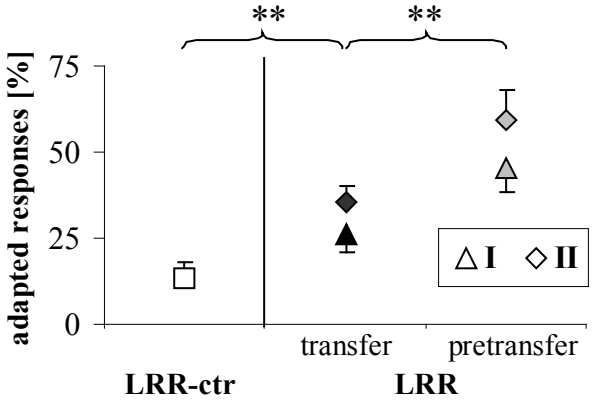


Fig. 5 Mean *PA* ± standard errors across subjects for the first adaptation episode of LRR-ctr, as well as for the first transfer episode and the preceding adaptation episode of LRR.

Figure 5 additionally shows *PA* during the two adaptation episodes that directly preceded the transfer episodes. Two-way ANOVA with the within-factors transfer Phase (I, II) and Episode (pretransfer, transfer) yielded significant effects of Phase ($F(1,11) = 17.721$; $p < 0.01$) and Episode ($F(1,11) = 15.147$; $p < 0.01$), confirming that the magnitude of transfer was less than complete. Calculated as

$$100 * \frac{PA_{Transfer}}{PA_{\mathrm{Pr}etransfer}}, \qquad (2)$$

the magnitude of transfer averaged 57.32% during first transfer and 59.39% during second transfer phase.

Figure 6A shows the *PA* of the first episode of the second transfer phase, separately for each of the eight targets from set B. Also shown are the predictions of a Gaussian model (cg. Eq. (1)): the light gray curve represents the tuning width of σ = 23° (Tanaka et al. 2009), the dark gray curve the optimal constant width of σ = 16° and the black curve a set of rotation-dependent widths (see Appendix). Figure 6B illustrates the goodness-of-fit for all three model versions, as well as for a linear rather than Gaussian model which we added for comparison purposes. Figure 6C and D show the corresponding results for the first episode of the first transfer phase.

One-way ANOVA of fitting errors from the second transfer phase, with the between-factor Model version (linear/ σ = 23°/ σ = 16°/ variable σ) yielded a significant effect of Model ($F(3,28) = 7.57$; $p < 0.001$). Post-hoc decomposition revealed significant differences between linear and σ = 16° ($p < 0.01$), linear and variable σ ($p < 0.001$), but not between linear and σ = 23° ($p > 0.05$). For fitting errors from the first transfer phase, the effect of Model just escaped statistical significance ($F(3,28) = 2.73$; $p = 0.063$).

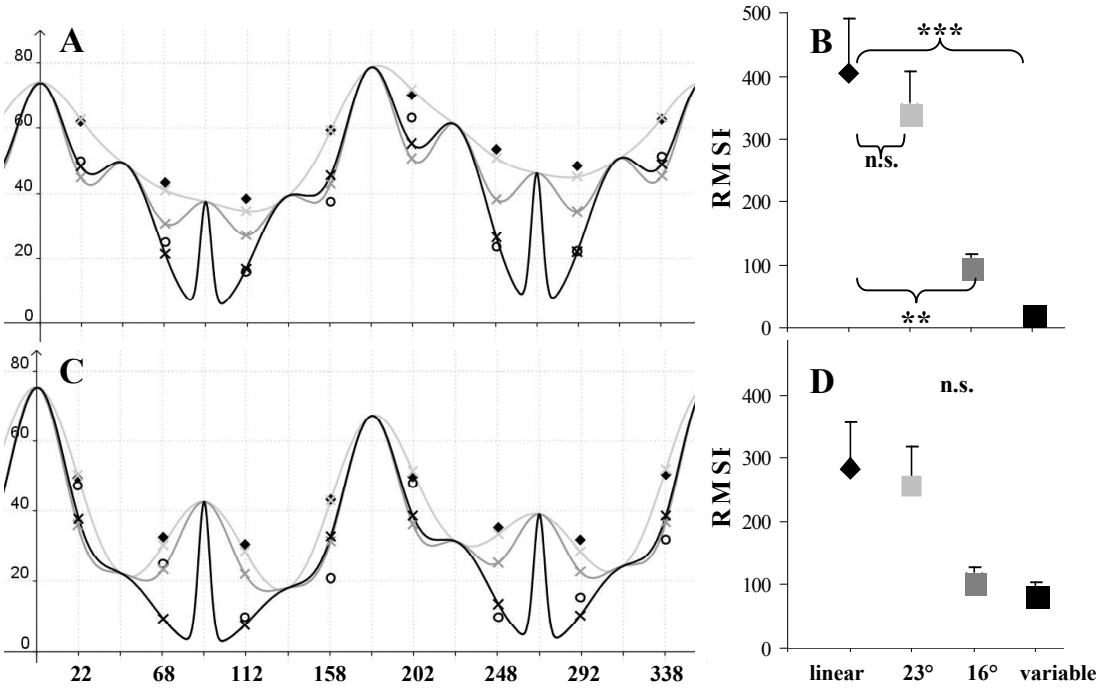


Fig. 6 Mean *PA* of the first episode in transfer phase II (**A**) and I (**C**) for each target direction (*white circles*), and the corresponding linear predictions (*black diamonds*). Predictions of the Gaussian model are shown for a tuning width of σ = 23° (*light gray line and crosses*), σ = 16° (*dark gray line and crosses*) and for varying σ (*black line and crosses*). Root mean square errors between experimental data and predictions are shown for transfer II (**B**) and transfer I (**D**).

4.5 Discussion

The present study scrutinized whether adaptation to left-right reversed vision could be based on similar, directionally tuned processes as adaptation to visual rotations. We confirmed that adaptation to a left-right reversal is achieved by concurrent, target-specific processes of the same type as previously described with visual rotations (Werner and Bock 2010). We further found that adaptation to a left-right reversal is less efficient than in control conditions which required the same adaptive change for all targets. This decrement could indicate that the tuning curves of neighboring targets overlap, or alternatively, that the neighboring processes mutually interfere.

We observed a transfer of adaptation from trained target set A to untrained target set B, with transfer magnitude increasing during the time-course of adaptation. At a first glance, this observation seems to replicate earlier findings about successful transfer (Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Krakauer et al. 2000); however, the situation in the present study is more complex. Whereas previous work required the same transformation to be used with new targets, our experiment called for a distinctly different, not yet practiced transformation. For example, group LRR learned a 180° rotation for the target at 0° and a -90° rotation for the target at 45°, and then had to produce the completely new rotation of -158° for the transfer target at 22°. Our modeling approach suggests that this new transformation was obtained through superposition of the neighboring trained tuning curves.

Previous work argued that training with eight evenly distributed targets is sufficient to establish generalized adaptation across all directions. Thus, one study reported 100% transfer to interposed targets after training with eight targets (Krakauer et al. 2000), and another study found adaptation not to improve with more than eight targets (Werner and Bock 2007). However, these data were yielded with rotated visual feedback, i.e., a distortion which required the same adaptive modification for all targets; in such a situation, it is difficult to distinguish between transfer due to generalization and transfer due to superposition of neighboring adapted modules. The present study uses a distortion which requires different adaptive modifications for different targets, and documents that adaptation did not generalize: transfer reached only about

60%, and could be quantitatively predicted as superposition of Gaussian tuned adaptive processes (Ghahramani et al. 1996; Tanaka et al. 2009).

The tuning width suggested by our fitting procedure may be specific for left-right reversals, since different tuning widths have been reported for force fields (Thoroughman and Shadmehr 2000; Donchin et al. 2003), grip force learning (Witney and Wolpert 2003) and different visual distortions (Ghahramani et al. 1996; Tanaka et al. 2009). Our results even predict tuning widths to depend on the size of rotation angle, since the best fit of our data was achieved when σ was allowed to vary between targets requiring 0°, 90°, and 180° rotation. The possible relationships between directionally tuned adaptive modules and similarly tuned neurons in posterior parietal cortex (Andersen et al. 1985) should be explored in future work.

In conclusion, the present study shows that adaptation to different directions emerges in a regional and interdependent fashion, and can be modeled as overlapping Gaussian tuned processes.

4.6 Appendix

To solve the Gaussian sum function in Eq. (1), we chose *i* to pass through 16 directions, i.e., from –180° to 495°, such as to accommodate the circular structure of the target array, and created the non-linear system of equations:

$$\sum_{i=-4}^{11} a_i \exp\left(-\frac{(-180-45*i)^2}{2\sigma^2}\right) - \overline{a}_{-4} = 0 \tag{3}$$

$$\sum_{i=-4}^{11} a_i \exp\left(-\frac{(-135-45*i)^2}{2\sigma^2}\right) - \overline{a}_{-3} = 0 \tag{4}$$

...

$$\sum_{i=-4}^{11} a_i \exp\left(-\frac{(495-45*i)^2}{2\sigma^2}\right) - \overline{a}_{11} = 0\,. \tag{18}$$

Here, $\overline{a}_i$ equals the mean *PA* of the three adaptation episodes preceding the second transfer phase at the direction *i**45°. Solving this system of equations for σ = 23° (Tanaka et al. 2009) yielded the light gray fit in Figure 5A.

Next, the above system of equations was solved for tuning widths from σ = 1° to 25° in 1° increments; the goodness of fit was best for σ = 16°, which corresponds to the dark gray curve in Figure 5A. The same procedure was then repeated while allowing σ to vary between targets requiring 0°, 90°, and 180° rotation, respectively. Goodness of fit was best with σ ≤ 3° for targets requiring no change, σ = 16° for those requiring a 180° rotation, and σ = 18° for those requiring a 90° rotation.

The linear fit was computed by a linear interpolation between *PA* of the trained target directions:

$$f(\theta) = \frac{(\overline{a}_i - \overline{a}_{i+1})}{(i*45-(i+1)*45)}\theta + \frac{(\overline{a}_i(i+1)*45 - \overline{a}_{i+1}i*45)}{((i+1)*45 - i*45)}$$

$$\text{for} \qquad i*45 \le \theta < (i+1)*45, \tag{19}$$

where *i**45° is the direction of the trained targets and $\overline{a}_i$ equals the mean *PA* of the last three adaptation episodes preceding the second transfer phase at the direction *i**45°.

For validation of our modeling approach, we calculated the model predictions for the first transfer phase as well, using the same σ values as for the second transfer phase (Figure 5C).

4.7 Acknowledgements

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5 Fourth study:
The effect of cerebellar cortical degeneration on adaptive plasticity and movement control

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(impact factor of journal 2009: 2.256)

5.1 Abstract

Clinical and neuro-imaging studies provide converging evidence that the cerebellum plays an important role for sensorimotor adaptation by participating in the adaptive process per se, and/or by evaluating motor performance errors as a prerequisite for adaptation. Recent experimental evidence suggests that error signals pertinent to adaptation are related to sensory prediction rather than to online corrections (Tseng et al. 2007). To further elucidate the role of the cerebellum, the present study uses a multiple regression approach to separate out three independent determinants of adaptive success. Seventeen patients with cerebellar atrophy but without extracerebellar lesions and 17 healthy, sex- and age-matched controls participated. Both subject groups performed center-out pointing movements before, during, and after exposure to 60° rotated visual feedback. From the registered data, we quantified four indicators of adaptive success (adaptive improvement, retention without feedback, intermanual transfer, and de-adaptation under normal feedback), as well as five measures of motor performance (reaction time, peak velocity, movement time, response variability, and ability for online error corrections). The variance of each adaptation indicator was then partitioned into three components, one related to subject group but not to motor performance, a second related to group *and* motor performance, and a third related to motor performance but not to group. In accordance with previous work, adaptation and motor performance were degraded in patients. The deficit was similar in magnitude for all four adaptation indicators, which suggests that adaptive recalibration rather than strategic control were affected in our patients. No adaptation indicator shared statistically significant variance with group alone; we therefore found no evidence for cerebellar circuitry dedicated to adaptation but not motor performance. Three indicators shared significant variance jointly with group and motor performance; this suggests that the cerebellar contribution to motor performance is related to adaptive success. All four indicators shared significant variance with motor performance alone; this indicates that *extra*cerebellar contributions to motor performance are also related to adaptive success. In conclusion, our data support the view that neural structures inside and outside the cerebellum are processing motor performance-related signals as a prerequisite for adaptation, but provide no evidence for a cerebellar structure related exclusively to adaptation.

5.2 Introduction

Since the pioneering theoretical work of Albus and Marr (Albus 1971; Marr 1969), the cerebellum has been considered a crucial brain structure for motor learning. Indeed, experimental evidence supports its contribution to the conditioning (Gerwig et al. 2003; Timmann et al. 2000; Woodruff-Pak 1997), habituation (Maschke et al. 2000), and scaling (Bloedel and Bracha 1997) of various reflexes. The cerebellum has also been implicated in a more complex form of motor learning, namely, *sensorimotor adaptation* to visual and mechanical distortions. This view is supported by clinical studies, which found that adaptation is often reduced or abolished in patients with cerebellar disease (Deuschl et al. 1996; Diedrichsen et al. 2005; Gauthier et al. 1979; Martin et al. 1996; Maschke et al. 2004; Tseng et al. 2007; Weiner et al. 1983). Further support comes from functional neuro-imaging studies, which observed an increase of cerebellar activity during an adaptation task (e.g., Flament et al. 1996; Graydon et al. 2005; Imamizu et al. 2000; Krakauer et al. 2003; Krebs et al. 1998; Lang et al. 1988).

A long-standing debate in literature focuses on the specific role played by the cerebellum during adaptation. According to one position, this brain structure is involved in the adaptive process per se, by storing an internal model of body and surrounds, which can be adaptively modified to compensate for imposed external distortions. According to the alternative position, the cerebellum monitors and controls the execution of movements, and thus provides performance-related signals as a crucial *prerequisite* for adaptation. In support for the first view, cerebellar patients show adaptation deficits even when executing ballistic responses, which are too fast for online error monitoring (Deuschl et al. 1996; Martin et al. 1996; Maschke et al. 2004; Tseng et al. 2007). In support for the second view, cerebellar activation in healthy subjects is more closely associated with performance errors than with adaptive progress (Flament et al. 1996). Another study favors a compromise between both above positions: adaptation was associated with widely distributed cerebellar activation which gradually decreased with practice, but also with focused activation near the posterior superior fissure which didn't decrease with practice, and which persisted even after equating for performance errors (Imamizu et al. 2000). The authors concluded that the distributed activation might reflect performance-related processes, while the focused activation might reflect the internal model.

A recent study (Tseng et al. 2007) compared adaptation under two conditions: when subjects executed ballistic movements which didn't allow online error corrections, and when they performed slower movements which did allow such corrections. They found no difference between conditions in healthy subjects, which indicates that adaptation is not driven by online response corrections, but rather by the mismatch between intended and perceived response, called "sensory prediction error". They also found no difference between conditions in cerebellar patients, which suggests that patients' adaptation deficits cannot be explained by impaired online corrections. This outcome doesn't distinguish between the above two positions, but it stipulates that performance-related signals provided by the cerebellum for adaptation would include sensory predictions rather than online corrections.

To further elucidate the role of the cerebellum, the present study uses a multiple regression approach to separate out three components of adaptive success: one related to cerebellar integrity but not to motor performance, the second related jointly to cerebellar integrity and motor control performance, and the third to motor performance but not cerebellar integrity. A significant contribution of the first component would support the existence of cerebellar circuitry dedicated to adaptive processing but not to motor performance. A significant contribution of the second component would reflect cerebellar mechanisms involved in the monitoring and control of movements - including sensory prediction, while a significant contribution of the third component would support the role of mechanisms for motor control which are spared in cerebellar degeneration.

5.3 Methods

Subjects

Seventeen patients and 17 control subjects participated after providing written informed consent. Both groups were matched in age (patients: 55.29 ± 10.34 years, control: 54.59 ± 8.57 years) and gender (8 females and 9 males each). All participants were right-handed, and took no medicine affecting the central nervous system. All control subjects were in good health, and had no history of neurological disease. Patients presented with forms of cerebellar cortical degeneration, that is, sporadic adult onset ataxia (SAOA), spinocerebellar ataxia type 6 (SCA6) and genetically

undetermined autosomal dominant cerebellar ataxia type III (ADCA III). Magnetic resonance imaging (MRI) revealed cerebellar atrophy with no extracerebellar lesions in all patients. Clinical examination showed a pure cerebellar syndrome in the majority of cases, with mild accompanying pallhypesthesia and/or hyperreflexia of the lower limbs in seven patients. Each patient's diagnosis, severity of ataxia, and extent of cerebellar atrophy are provided in Table 1. On the average, cerebellar volume was

Patient	Age	Sex	Diagnosis	Volume	Ataxia	
					Total	Upper-limb
HS	66	M	SAOA	6.5*	20/56	7/24
FS	59	F	SAOA	7.2*	15/56	5/24
MI	66	F	SAOA	8.0	18/56	7/24
EE	45	F	SAOA	6.7*	19/56	8/24
US	39	F	SAOA	5.1*	23/56	10/24
KT	42	M	ADCAIII	6.4*	16/56	5/24
DB	48	M	SAOA	6.6*	19/56	5/24
HG	65	M	SCA 6	7.2*	24/56	10/24
HM	67	M	SAOA	7.7	5/56	2/24 (left only)
DS	49	M	SCA 6	7.9	5/56	2/24
PK	65	M	ADCAIII	8.0	14/56	6/24
PF	47	M	SAOA	6.3*	14/56	5/24
CW	42	F	ADCAIII	4.7*	7/56	5/24
RB	53	F	SAOA	8.2	12/56	4/24
WA	56	F	SCA6	7.6	18/56	8/24
FR	61	F	ADCAIII	9.0	0/56	0/24
KF	70	M	SCA 6	6.8*	13/56	3/24

Tab. 1 Patients' characteristics: Age, sex (F-female; M-male), diagnose (ADAC III - autosomal dominant cerebellar ataxia type III; SAOA - sporadic adult onset ataxia; SCA6 - spinocerebellar ataxia type 6), cerebellar volume as percent of intracranial volume (asterisks mark values less than mean minus standard deviation of healthy individuals), and total as well as upper-limb ataxia scores from SARA (Schmitz-Hubsch et al. 2006a). Note that subscores of upper-limb ataxia of the right and left arm were summed up, and no means were taken as in the original publication.

7.1 ± 1.5% of total intracranial volume in female, and 7.1 ± 0.7% in male patients; the corresponding values for healthy individuals are 8.2 ± 0.7% in females and 8.0 ± 0.7% in males (Dimitrova et al. 2006). The cerebellar volume of individual patients correlated inversely with their severity of ataxia ($r = -0.67$, $p < 0.05$). The experimental protocol was pre-approved by the authors' local Ethics Committee.

Procedure

Seated subjects were instructed to point quickly and accurately at visual targets. As shown schematically in Figure 1a, they watched a computer screen (S) through a mirror (M), such that the virtual image of the screen coincided with the horizontal surface of a digitizing tablet (T). A starting dot appeared for 0.5 to 3.0 s in the center of the virtual display, and was then replaced by one of eight possible target dots, located 45° apart along an imaginary circle of 10 cm radius about the center. 2 s later the target was replaced by the starting dot, irrespective of how accurately the subjects had pointed. The starting dot remained on for 0.5 to 3.0 s, then the next target appeared, etc. Subjects held a digitizing pen in their hand, and pointed at each target and back by moving the pen across the digitizing tablet. They were unable to see their arm, due to the mirror and surrounding shrouds; however, pen position was registered with a resolution of 0.3 mm and 60 Hz, and was displayed on the screen as a cursor to provide visual feedback about instantaneous hand position. Thus, the subjects' task was essentially to move the cursor towards each target and back.

The experiment was subdivided into episodes of 30 s duration, or about 6-12 target presentations, separated by rest breaks of about 4 s. Depending on the particular episode, subjects used either their right or their left hand for pointing, and visual feedback about hand position was either veridical or rotated 60° clockwise about the starting dot. The experiment began with one *familiarization* episode, in which subjects pointed with their right hand under veridical visual feedback. Next came the *baseline* phase, with one episode using the left, and then three episodes using the right hand, again under veridical feedback. The subsequent *adaptation* phase consisted of 20 episodes with the right hand, in which visual feedback was rotated by -60° to induce adaptation. Subjects returned one day or one week later[4] for the *reten-*

[4] The patients also took part in another study where different pause lengths were part of the test design. We did not anticipate an effect of pause length in our study, since retention of the adapted state remains nearly complete even after a 1-month pause (Bock et al. 2001).

tion phase of five episodes, using again the right hand under rotated feedback. Next came the *intermanual transfer* phase of two episodes, using the left hand under rotated feedback, followed by a single *refresh* episode, using the right hand under rotated feedback. Finally came the *de-adaptation* phase of five episodes, using the right hand under veridical feedback. The total testing time including instructions was about 20 minutes on the first, and about 10 minutes on the second day.

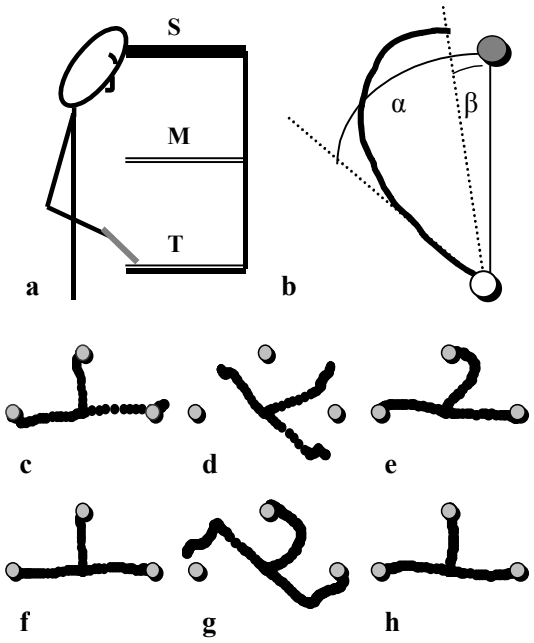

Fig. 1 **a** Scheme of experimental apparatus with display screen (S), mirror (M), and digitizing tablet (T). **b** Angles used for calculating the online correction ability (CA): White and grey dots represent starting point and target, the black line shows a sample movement path, α is the initial pointing error (150ms after movement onset), β the final error, and (α-β) is the correction angle. CA was calculated as the coefficient of determination between the correction angle and α. **c-e** Sample cursor paths towards three of the eight possible targets in a patient with diffuse cerebellar atrophy, registered during the baseline phase (c), the beginning of the adaptation phase (d), and the end of the adaptation phase (e). **f-h** corresponding sample movement paths from a healthy control subject.

Data analysis

To quantify the time-course of adaptive improvement, we determined the *initial error* of each response as the angular difference between cursor and target direction 150 ms after response onset, i.e., before feedback-based corrections could become effective. Response onset was defined as the first sample after movement speed exceeded 32mm/s; response end was determined accordingly. The mean initial errors of each subject and episode were submitted to an analysis of variance (ANOVAs) with the between-factor Group (patient, control) and the within-factor Episode; Huynh-

Feldt-adjustments to the degrees of freedom were applied when necessary to compensate for heterogeneity of variances.

For further data reduction, we calculated each subject's adaptive success as adaptive improvement AI, adaptive retention AR, adaptive transfer AT, and de-adaptation DA:

$$AI\ [°] = 60 - B + A, \quad (1)$$

$$AR\ [°] = 60 - B + R, \quad (2)$$

$$AT\ [°] = 60 - B + T, \quad (3)$$

$$DA\ [°] = D - B, \quad (4)$$

where B and A are the mean initial error of the last three baseline and the last three adaptation episodes, respectively, and R, T, and D are the initial errors of the first retention, transfer, and de-adaptation episode, respectively.

We further determined several measures of each subject's motor performance. To quantify the speed of responding, we calculated the means of reaction time RT, peak velocity PV, and movement time MT during the adaptation phase. To quantify the consistency of the initial, ballistic portion of responses, we calculated response variability RV as the standard deviation of initial errors about their respective mean. This measure was calculated only from the last three baseline episodes, to ensure that it is not contaminated by variability related to adaptive change.

To quantify the ability for online error corrections, we calculated the final error as the angular difference between cursor and target direction at the end of each movement, and defined the difference between initial and final errors as correction angle (a - b in Figure 1b). Subjects with good correction ability should produce large correction angles when initial errors are high, and small correction angles when initial errors are low; in contrast, subjects with poor correction ability should produce correction angles, which are not closely related to initial errors. We therefore quantified each subject’s correction ability CA as the coefficient of determination between correction angles and initial errors. To obtain robust values, we calculated CA from data of the adaptation phase, where initial errors were large; however, we excluded the very first adaptation episode, since some movements in that episode looked quite erratic. We considered it justifiable to determine CA, even though online corrections

do not appear to affect adaptive success (Tseng et al. 2007), since CA could arguably reflect the processing of prediction errors as well (see "Introduction" and "Discussion", Chapters 5.2 and 5.5).

The relationship between adaptive success, subject group, and motor performance was scrutinized with a multiple linear regression approach. To this end the total variance of each adaptation indicator (AI, AR, AT, DA) was partitioned into several components as shown in Figure 2. The variance shared between the adaptation indicator (A) and the group (G) equals the coefficient of determination between A and G, $R^2(G)$, represented in Figure 2 by the common area $Var_G + Var_J$. Furthermore, the variance shared between A and the performance measures CA, RV, RT, PV, MT equals the multiple coefficient of determination $R^2(P)$, reflected in Figure 2 by the common area $Var_J + Var_P$. Likewise, the variance shared between A, G, and P corresponds to the multiple coefficient of determination $R^2(PG)$, represented in Figure 2 as $Var_G + Var_J + Var_P$. A detailed explanation of the partitioning of variances can be found in Bock and Girgenrath (2006).

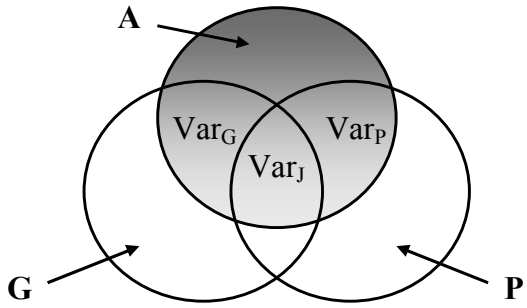

Fig. 2 The concept of common and unique variances. Circle A represents the variance of an adaptation indicator: AI, AR, AT, or DA respectively. Circle G pictures the variance of Group and circle P the shared variance of the performance measures (CA, RV, RT, PV, and MT). The overlapping areas indicate the variance of A shared with G only (Var_G), with P only (Var_P), and with G and P jointly (Var_J).

Consequently, the variance of A can be partitioned into a component Var_G shared with group but not with motor performance, a component Var_J shared jointly with group and motor performance, and a component Var_P shared with motor performance alone:

$$Var_G = R^2_{PG} - R^2_P, \quad Var_J = R^2_G + R^2_P - R^2_{PG}, \quad Var_P = R^2_{PG} - R^2_G, \tag{5}$$

If e.g. $R^2_{PG} - R^2_P$ is significant as analyzed by the significance test of the Pearson product-moment correlation, then Var_G makes a decisive contribution to A.

5.4 Results

Figure 1 shows original registrations of cursor paths produced by a patient (c-e), and by a control subject (f-h). Paths registered during the baseline phase (c, f) are straight and well aimed. At the onset of adaptation (d, g), paths are misdirected by about 60°, as expected due to the imposed visual rotation; the paths curve back towards the targets later on in the control subject but not in the patient, suggesting that online error corrections are more pronounced in the control subject. Near the end of adaptation (e, h), the paths become again straighter and more accurate, particularly in the control subject.

The above observations are confirmed and expanded by Figure 3. The initial error across subjects from the control and the patient group was near zero during the baseline phase, became abruptly negative at the onset of adaptation, and then gradually returned towards zero, more so in controls than in patients. The group difference attained at the end of the adaptation phase persisted throughout the subsequent retention, transfer, and refresh phases, and then gradually decreased during the deadaptation phase. These observations were confirmed statistically. An ANOVA of the adaptation phase yielded significant effects of Group ($F(1,31) = 18.78$; $p < 0.001$), Episode ($F(17,526) = 45.19$; $p < 0.001$) and Group × Episode ($F(17,526) = 3.71$; $p < 0.001$). An ANOVA of episodes 22 to 33 (i.e., late adaptation to early de-

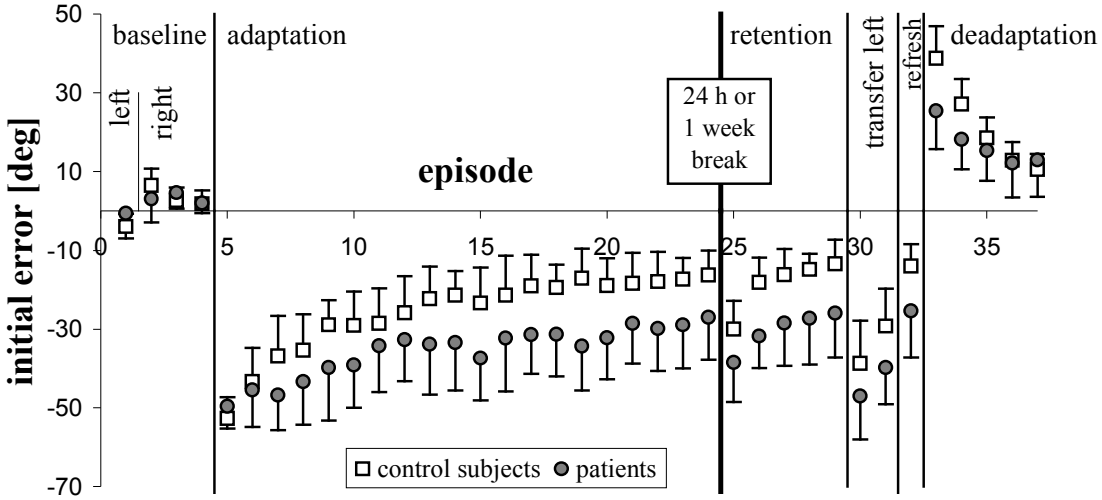

Fig. 3 Initial pointing error for all experimental episodes in patients (*gray*) and controls (*white*); *left* indicates episodes in which subjects used their left arm for pointing. Symbols represent across-subject means, and bars the pertinent standard deviations.

adaptation) yielded significant effects for Group ($F(1,32) = 22.78$; $p < 0.001$) and Episode ($F(11,352) = 314.13$; $p < 0.001$) but not for their interaction. Finally, an ANOVA of the de-adaptation phase yielded a significant effect of Group ($F(1,32) = 5.22$; $p < 0.05$), Episode ($F(3,86) = 111.90$; $p < 0.001$) and their interaction ($F(3,86) = 15.95$; $p < 0.001$).

Even though Bock et al. found the adapted state to remain nearly complete after a one-month pause (2001), one might argue that this is not the case for patients. However additional ANOVAs with the between-factors Group (patient, control) and Pause length (day, week) yielded no significant effects for Pause length (Retention: $F(1,30) = 0.00$; $p > 0.05$, Transfer: $F(1,30) = 0.07$; $p > 0.05$, De-adaptation: $F(1,30) = 0.49$; $p > 0.05$), thus discarding the above argument.

	mean ± sd		t(32)	correlations with	
	controls	patients		patients` ataxia	patients` volume
AI	39.2 ± 5.4	28.1 ± 9.2	-4.3***	-0.674*	0.348*
AR	26.3 ± 7.7	18.2 ± 10.5	-2.5*	-0.443*	0.166
AT	17.7 ± 11.4	9.7 ± 10.8	-2.1*	-0.303	0.123
DA	35.1 ± 8.2	22.2 ± 10.0	-4.1***	-0.534*	0.306
CA	0.9 ± 0.1	0.7 ± 0.3	-3.2**	-0.515*	0.077
RV	11.1 ± 8.0	14.6 ± 11.6	1.0	0.112	0.080
RT	0.4 ± 0.1	0.5 ± 0.1	3.3**	0.556*	-0.069
PV	246.8 ± 64.6	202.6 ± 77.6	-1.8	-0.237	0.163
MT	1.1 ± 0.2	1.4 ± 0.4	2.2*	0.355*	-0.211

Tab. 2 Indices of adaptation (top part) and measures of movement performance (bottom part) in healthy controls and in cerebellar patients. The third data column presents the outcome of group comparisons with t-tests, and the last two columns the correlations of patients' findings with ataxia scores and cerebellar volume. Symbols ***, **, and * indicate p<0.001, p<0.01, and p<0.05, respectively, and the absence of a symbol indicates p>0.05.

The top part of Table 2 summarizes our findings regarding the four adaptation indicators. All indicators were significantly lower in patients than in control subjects, thus confirming the existence of adaptation deficits in cerebellar disease (see “Intro-

duction", Chapter 5.2). Within the patient group, three indicators correlated significantly with the ataxia score, and one with cerebellar volume. The bottom part of Table 2 summarizes our findings regarding the five motor performance measures. Patients show significantly poorer performance than controls on three of those measures, and the same three measures were also significantly correlated with patients' ataxia scores. The correlation with cerebellar volume was not significant for any measure.

Table 3 summarizes the outcome of our multiple regression analyses. The variance shared with diagnosis but not motor performance (Var_G) was not significant for any adaptation indicator, the variance shared with diagnosis *and* motor performance (Var_J) was significant for three, and the variance shared with motor performance alone (Var_P) was significant for all four indicators. We noticed that some of our subjects' responses were slow, and terminated only after target disappearance, which could potentially bias our CA and MT scores. We therefore decided to replicate the regression analyses using only responses which terminated in time. One control subject and four patients had to be excluded from this replication because of too few acceptable movements. After sorting out all movements with (MT + RT) > 2 s there was no more difference between groups for MT ($t(27) = -0.46$, $p > 0.5$). However, the remaining data yielded exactly the same pattern of significant and non-significant variance components as in Table 3.

	Var_G	Var_J	Var_P
AI	0.0123	0.3530***	0.2600**
AR	0.0001	0.1687*	0.3883***
AT	0.0449	0.0744	0.1719*
DA	0.0327	0.3168***	0.1691*

Tab. 3 Outcome of linear regression analyses. The total variance of each adaptation indicator was partitioned into a component Var_G shared with subject group but not with motor performance, a component Var_J shared jointly with group *and* motor performance, and a component Var_P shared with motor performance alone. Symbols have the same meaning as in Tab. 2.

One might argue that our performance measures are not independent from adaptation since they were taken during the adaptation phase. We therefore recalculated CA, RT, PV, and MT using the baseline phase, and repeated the multiple regression

analysis: the significance pattern didn't change, which suggests that our performance measures were not corrupted by adaptation ability.

One might further argue that the observed relationship between motor performance and adaptation indicators is artefactual: it would also emerge if this relationship didn't exist on a subject-to-subject basis, as long as the patients as a group would exhibit both a poorer motor performance and a poorer adaptation than controls as a group. Figure 4 illustrates for one performance and one adaptation score that this was not the case: patients and controls overlapped with respect to AI, as well as with respect to MT. More importantly, the multiple regression between motor performance and adaptation indicators remained significant even when the analysis was limited to the patient group only (R^2_{AI} = 0.6494*, R^2_{AR} = 0.6515*, R^2_{AT} = 0.2955, and R^2_{DA} = 0.7487**).

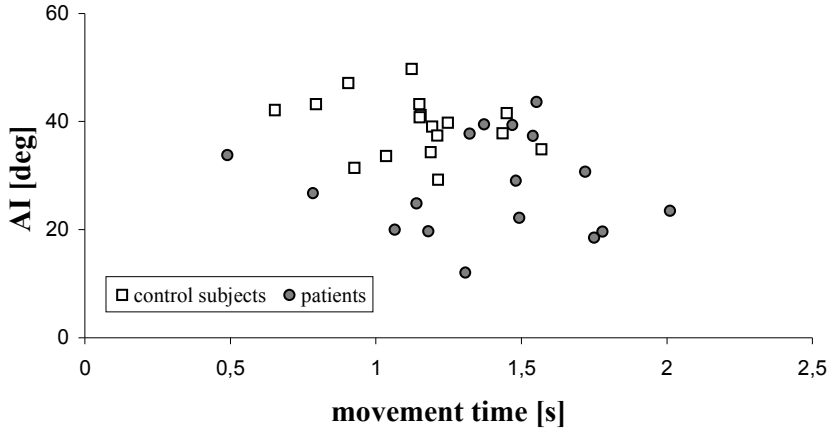

Fig. 4 Relationship between movement time and adaptive improvement AI in patients (*gray*) and controls (*white*). Each symbol represents one subject.

Since the above analyses included five different measures of motor performance, we explored which of them are crucial for the significance pattern in Table 3, by replicating the regression analyses with different subsets of those measures. We found that the significance pattern persisted as long as the analyses included MT and CA, or MT and RT. We therefore concluded that MT, CA, and RT are indicators of adaptive success. These are the same three measures which differed significantly between patients and controls, and which correlated significantly with patients' ataxia scores (see Table 2). As an example, Figure 4 depicts the relationship between MT and AI in both subject groups.

5.5 Discussion

The present study evaluated adaptive success and motor performance in patients with cerebellar cortical degeneration, and in healthy control subjects. In accordance with literature (Deuschl et al. 1996; Diedrichsen et al. 2005; Gauthier et al. 1979; Martin et al. 1996; Maschke et al. 2004; Tseng et al. 2007; Weiner et al. 1983), we found that patients adapted less well than controls. Also in accordance with previous work (Martin et al. 1996; Maschke et al. 2004; Weiner et al. 1983), the deficit was not limited to the adaptation phase, but rather continued undiminished throughout the retention and transfer into the de-adaptation phase. Such a persistence of the deficit is interesting, as it allows an insight into the underlying pathology. It is thought that *adaptive improvement* is based on two distinct processes, a recalibration of sensory-to-motor transformation rules, and strategic control by anticipations, associative stimulus-response pairings, and other workaround schemes; in contrast, *retention*, *transfer*, and *de-adaptation* are thought to reflect recalibration alone (Bock 2005; McNay and Willingham 1998; Redding 1996). If so, the persistence of an adaptation deficit in our patients would indicate that recalibration but not strategic control is impaired by cerebellar degeneration.

Besides adaptive success, movement performance was also degraded in our patients. In accordance with literature, we found an increase of reaction and movement time, less efficient online error corrections, but normal peak movement velocity (Bonnefoi-Kyriacou et al. 1998; Holmes 1917; Hore et al. 1991; Tseng et al. 2007). Previous work further reported an increase of movement variability (Martin et al. 1996; Timmann et al. 1999; Tseng et al. 2007) which didn't reach statistical significance in our study. This is probably so because our patients' ataxia was relatively mild (see Table 1); cerebellar areas related to upper-limb ataxia (Martin et al. 1996) may not have been profoundly affected in all our patients.

The main purpose of the present study was to scrutinize the interrelation between patients' deficits of adaptation and of motor performance. We therefore partitioned the variance of each adaptation indicator into three components. Var_G was related to subject group but not motor performance, and didn't reach statistical significance for any indicator; we therefore have no evidence for the existence of cerebellar circuitry dedicated to adaptation but not to motor performance. Var_J was related jointly to

group and motor performance, and Var_P to motor performance alone. The latter two components were significant for most or all adaptation indicators, which suggests that cerebellar and extracerebellar brain regions involved in the monitoring and control of movements also contributed towards adaptive success. This contribution could be interpreted in two ways: the respective brain regions could be involved in motor performance alone and send their output to adaptive mechanisms located elsewhere, or they could be involved in both functions, motor performance *and* adaptation.

The above conclusions are pertinent to the two positions on the role of the cerebellum, as outlined in the Introduction. Our findings are in accordance with one of the views, which holds that the cerebellum provides performance-related signals as a prerequisite for adaptation. They also agree with a compromise between both views, which posits that adaptation and motor performance are processed in identical or highly interlinked cerebellar structures. However, our findings do not support the pure version of the other view, according to which the cerebellum contains circuitry dedicated to adaptation but *not* motor performance.

Our analyses indicate that three measures of motor performance were associated with adaptive success. One of them represented the efficiency of online error corrections. The simple correlation between adaptation indicators and this measure ranged between 0.46 and 0.71, which is similar to the correlations reported before (Tseng et al. 2007). The correlations were significant in the present work ($p<0.01$) but not in the previous study, possibly because the variables were defined somewhat differently, and/or because the sample size was larger in the present ($n=2*17$) than in the previous study ($n=2*7$). The existence of sizable correlations should not be taken as evidence that adaptation is driven by online response corrections; this surmise has been convincingly refuted before, and replaced by the view that adaptation is driven by sensory prediction errors (Tseng et al. 2007). Instead, the observed correlation could reflect the dependence both of adaptive success and of online corrections on a common causal factor, e.g., cerebellar function.

The present study not only assessed the role of the cerebellum in sensorimotor adaptation, but also provided evidence for adaptive mechanisms located outside the cerebellum. As stated above, the significance of Var_P suggests that extracerebellar brain regions related to motor performance either were involved in adaptation as well, or sent their output to other extracerebellar areas dedicated to adaptation. Reasonable

candidates for such areas are the inferior parietal and the dorsal premotor cortex: a recent neuro-imaging study which controlled for error-related brain activity found significant extracerebellar activation only in these two areas (Girgenrath et al. 2007).

5.6 Acknowledgements

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6 Fifth study:

Visuomotor *adaptive improvement* and *aftereffects* are impaired differentially following cerebellar lesions in SCA and PICA territory

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Reference

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(impact factor of journal 2009: 2.256)

6.1 Abstract

The aim of the present study was to elucidate the contribution of the superior and posterior inferior cerebellum to adaptive improvement and aftereffects in a visuomotor adaptation task. Nine patients with ischemic lesions within the territory of the posterior inferior cerebellar artery (PICA), six patients with ischemic lesions within the territory of the superior cerebellar artery (SCA) and 17 age-matched controls participated. All subjects performed center-out reaching movements under 60° rotation of visual feedback. For the assessment of aftereffects, we tested retention of adaptation and de-adaptation under 0° visual rotation. From this data we also quantified five measures of motor performance. Cerebellar lesion-symptom mapping was performed using magnetic resonance imaging (MRI) subtraction analysis. Adaptive improvement during 60° rotation was significantly degraded in PICA patients and even more in SCA patients. Subtraction analysis revealed that posterior (Crus I) as well as anterior cerebellar regions (lobule V) showed a common overlap related to deficits in adaptive improvement. However, for aftereffect measures as well as for motor performance variables only SCA patients, but not PICA patients showed significant differences to control subjects. Subtraction analysis showed that affection of lobules V and VI were more common in patients with impaired retention and de-adaptation, respectively. Data shows that areas both within the superior and posterior inferior cerebellum are involved in adaptive improvement. However, only the superior cerebellum including lobules V and VI appears to be important for aftereffects and therefore true adaptive ability.

6.2 Introduction

It has been argued in the past that sensorimotor adaptation depends on the integrity of the cerebellum, since patients with cerebellar disease show impaired adaptation to force fields (Maschke et al. 2004; Smith and Shadmehr 2005) and visual distortions while walking (Morton and Bastian 2004), pointing (Gauthier et al. 1979; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008), or performing ballistic elbow flexion and extension movements (Deuschl et al. 1996). Not only adaptive improvement, that is the reduction of errors during adaptation phase, but also aftereffects (Maschke et al. 2004; Morton and Bastian 2004; Smith and Shadmehr 2005; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008) and generalization (Morton and Bastian 2004) were found to be degraded. Aftereffect tests such as de-adaptation, retention or catch trials (that is single trials without perturbation during the adaptation phase) are commonly conducted to distinguish true adaptation or recalibration of sensory-to-motor transformation rules from adaptive improvement. The latter is thought to be achieved by recalibration on the one hand and strategic control such as cognitive updating of perceived feedback positions on the other hand. Since strategic control is thought to be short-lived and task-specific, it exclusively effects adaptation phase and has no impact on post adaptation phases or catch trials (Bock 2005; McNay and Willingham 1998; Redding et al. 2005; Redding and Wallace 1996; Werner and Bock 2007). In accordance with this reasoning sensorimotor recalibration and not just strategic planning is impaired in cerebellar patients.

Although there is general agreement that the cerebellum is involved in true sensorimotor adaptation, it is still under debate which specific parts of the cerebellum contribute. Several functional brain imaging studies in healthy human subjects have reported cerebellar activation both in visuomotor and force field adaptation tasks. The majority of studies report activations of the superior parts of the cerebellum (in particular in lobules IV, V and VI) (Della-Maggiore and McIntosh 2005; Diedrichsen et al. 2005; Imamizu et al. 2003; Imamizu et al. 2000; Seidler and Noll 2008; Seidler et al. 2006; Shadmehr and Holcomb 1997). One of these studies did not cover the more inferior parts of the cerebellum and, therefore, cannot exclude additional contributions of these parts of the cerebellum (Shadmehr and Holcomb 1997). The studies, which covered the entire cerebellum, are partly contradictory. Some studies report

adaptation-related activity in the superior cerebellum only (Della-Maggiore and McIntosh 2005; Seidler and Noll 2008; Seidler et al. 2006), whereas others found activation both in the superior and the posterior inferior cerebellum (lobules VIIB and VIII; Diedrichsen et al. 2005; Nezafat et al. 2001). It has to be noted, however, that not all studies carefully controlled for cerebellar activation related to motor performance such as hand acceleration or online motor corrections, which also have been shown to activate the superior (Diedrichsen et al. 2005; Grafton et al. 2008; Seidler et al. 2004), but also inferior parts of the cerebellum (lobule VIII; Diedrichsen et al. 2005).

The comparison of patients with ischemic stroke within the territory of the superior cerebellar artery (SCA) and the posterior inferior cerebellar artery (PICA) is a useful human cerebellar lesion condition to further elucidate the contribution of the superior and inferior cerebellum to sensorimotor adaptation. The SCA commonly supplies the anterior lobe (lobules I-V) and the more superior parts of the posterior lobe (lobules VI and Crus I), whereas the PICA commonly supplies the more inferior parts of the posterior lobe (lobules Crus II-X). Vascular territories, however, are variable and PICA strokes can involve Crus I (Timmann et al. 2009 for recent review).

As yet, two human vascular cerebellar lesion studies have assessed visuomotor adaptation. These studies have revealed contradictory results. One single-case study found a marked adaptation deficit following an SCA lesion (Pisella et al. 2005); however the other, well-cited study claimed that PICA lesions result in adaptation deficits but intact motor performance (Martin et al. 1996). To clarify this issue, we decided to compare motor performance and visuomotor adaptation in a larger sample of patients with either PICA or SCA territory involvement.

6.3 Methods

Subjects

We acquired data from fifteen patients with unilateral focal cerebellar lesions (mean age 57.3 ± 15.1 years; 3 female, 12 male). Nine patients had ischemic infarction within the PICA territory. Mean age in this patient group was 55.8 ± 10.3 years, mean time since lesion was 15.0 months, and their mean score on the Scale for the Assessment and Rating of Ataxia (Schmitz-Hubsch et al. 2006) was 1.7. Six patients

presented with ischemic infarction within the SCA territory. Their mean age was 59.5 ± 21.3 years, mean time since lesion was 17.7 months, and their mean ataxia score was 3.2. Thus, the magnitude of ataxia was mild in both patient groups. A general survey of patients' clinical and lesion data is given in Table 1. The location and extent of cerebellar lesions was defined from MRI data sets, as summarized in Table 2. MRI revealed no extra-cerebellar lesions in any patient.

Patient	Age	Sex	Cerebellar disorder	Duration of disease	Side	Volume	Ataxia rating scale		
							Total	Upper-limb	
								right	Left
CZ	41	F	PICA	19	L	0.4	0	0	0
FL	59	M	PICA	8	L	1.7	0	0	0
GE	59	M	PICA	13	R	9.9	0	0	0
MT	42	M	PICA	20	R	22.8	0	0	0
RK	46	M	PICA	19	L	11.9	0	0	0
SC	69	M	PICA	18	R	10.3	6	1	1
WS	57	M	PICA	15	R	31.4	2	0	0
JM	64	M	PICA	7	L	22.7	1	0	0
KM	65	M	PICA	16	L	30.5	6	0	3
HG	67	M	SCA	0	L	2.6	4	1	2
JL	18	F	SCA	12	L	1.0	0	0	0
KW	75	M	SCA	46	L	5.3	7	0	2
LR	72	M	SCA	11	R	1.2	2	1	0
LZ	69	F	SCA	22	R	0.3	4	0	1
MM	56	M	SCA	15	L	1.1	2	0	0

Tab. 1 Basic characteristics of patients in the present study: Age, sex (F-female; M-male), cerebellar disorder (PICA - infarct of posterior inferior cerebellar artery; SCA - infarct of superior cerebellar artery), duration of disease (time since lesion in months), side (R-right, L-left), volume of the lesion (in cubiccentimeters), and total as well as upper-limb ataxia scores from SARA (Scale for the assessment and rating of ataxia; Schmitz-Hubsch et al. 2006). Note that subscores of upper-limb ataxia of the right and left arm were summed up, and no means were taken as in the original publication.

Patient	Vermis	Hemisphere		Nuclei
		Paravermal	Lateral	
CZ	n.a.	n.a.	l: CRI, CRII	n.a.
FL	VIIAt, VIIB, VIIIA	l: CRII, VIIB, VIIIA, VIIIB, IX	n.a.	n.a.
GE	CRII, VIIAt, VIIB, VIIIB	r: CRI, CRII, VIIB, VIIIA, VIIIB	r: CRI, CRII, VIIB, VIIIA	(r: NI) r: ND
MT	n.a.	r: CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX	r: CRI, CRII, VIIB, VIIIA, VIIIB	n.a.
RK	VIIAt, VIIB, VIIIA, VIIIB, IX, X	l: (CRI), CRII, VIIA, VIIB, VIIIA, VIIIB, IX	l: CRI, CRII, VIIB, VIIIA, VIIIB	l: ND p
SC	VIIAt, VIIB, VIIIA, VIIIB, IX	r: CRII, VIIB, VIIIA, VIIIB, IX	r: CRII, VIIB, VIIIA, VIIIB	n.a.
WS	n.a.	r: CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX	r: VI, CRI, CRII, VIIA, VIIB, VIIIA, VIIIB, IX	r: ND p
JM	n.a.	l: (CRI), CRII, VIIB, VIIIA, VIIIB	l: CRI, CRII, VIIB, VIIIA, VIIIB	(l: ND)
KM	VIIAt, VIIB, VIIIA, VIIIB, IX, X	l: CRI, CRII, VIIB, VIIIA, VIIIB, IX	l: CRI, CRII, VIIB, VIIIA, VIIIB	(l: ND)
HG	n.a.	l: IV, **V**, **VI**	l: VI, CRI, CRII	n.a.
JL	n.a.	l: IV, **V**, **VI**	(l: VI)	(l: ND)
KW	III, IV, V, VI	l:**V**, **VI**	n.a.	(l: NI)
LR	n.a.	r: **V**, **VI**	n.a.	(r: ND)
LZ	n.a.	r: (**V**), **VI**	(r: VI, CRI)	n.a.
MM	n.a.	l: **V**, **VI**	l: VI	n.a.

Tab. 2 Cerebellar lesion site: Cerebellar lobules are named according to Schmahmann et al. (2000). R = right side, l = left side; NI = interposed nucleus, ND = dentate nucleus; n.a. = not affected, p = posterior part of dentate, brackets indicate partial lesions. Common lesions sites in SCA patients are marked in bold letters.

A group of 17 healthy, adult volunteers (mean age 54.6 ± 8.6 years; 8 females, 9 males) with no history of neurological disease served as controls. Their data have already been presented in our preceding study (Werner et al. 2008). All patients and controls were right-handed, and didn't use any drugs affecting the nervous system. None of the subjects had prior experience in visuomotor research. The authors' local Ethics Committee had approved the procedure of the experiment, and all subjects gave written informed consent.

Visuomotor adaptation task

As in our previous study (Werner et al. 2008), subjects sat in front of a digitizing tablet holding a pen as shown in Figure 1. They watched a computer screen through a horizontally mounted mirror that projected the image of the screen onto the tablet. The mirror and surrounding shrouds prevented the sight of the arm. A central starting dot and one of eight possible target dots appeared alternately on the screen. The starting dot remained on for 0.3 to 0.5 s, and was then replaced by one of the target dots, according to a random sequence. The targets were equally distributed on an imaginary circle of 10 cm radius about the centre, and each lit up for 2.0 s. All subjects were instructed to move the pen as accurately and quickly as possible from the starting dot to the target and back. The position of the digitizing pen was registered (resolution: 0.3 mm, 60 Hz), and displayed on the screen as a cursor to provide visual feedback about momentary hand position.

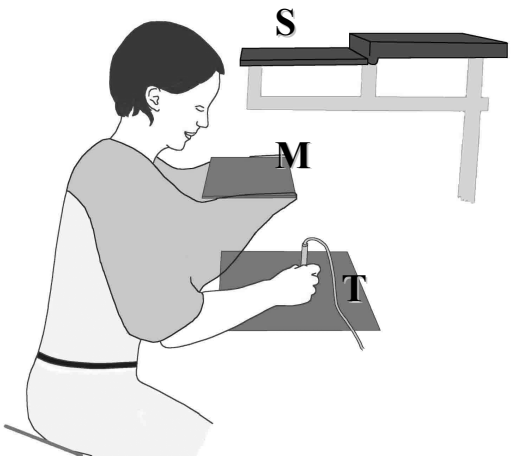

Fig. 1 Scheme of experimental apparatus with display screen (S), mirror (M), and digitizing tablet (T).

The experiment was subdivided into episodes of 30 s duration, separated by rest breaks of about 5 s. Within one episode, six to twelve targets were presented. If not stated otherwise, subjects pointed with their dominant, right hand. All were familiarized with the experimental set-up by performing one episode under veridical visual feedback, i.e., pen and cursor position coincided. Data registration began with a *baseline* phase of four episodes, again under veridical feedback, with the left hand used during the first of those episodes. The subsequent *adaptation* phase consisted of 20 episodes, in which visual feedback was rotated by -60° about the starting dot. After a one-day to one-week break subjects returned and performed five episodes in a retention phase, once again under -60° rotated feedback. This was followed by two episodes of an *intermanual transfer* phase using the left hand, and one *refresh* episode using the right hand, again under rotated visual feedback. Finally came a *de-adaptation* phase of five episodes under veridical visual feedback. The whole experiment including instructions lasted about 20 minutes on the first, and about 10 minutes on the second day.

Even though all patients presented with unilateral lesions either in the right or left cerebellum, they all conducted the greatest part of the experiment with their dominant right hand. This is justified by the fact that even for healthy subjects visuomotor adaptation with the right hand is faster, independent of the subjects´ handedness (Chase and Seidler 2008). Since we still had the possibility to analyze the effect of lesion laterality (see below), we chose to keep the task as practicable as possible for the cerebellar patients.

Data analysis

Subjects' responses were quantified as in our previous study (Werner et al. 2008). We determined the *initial error* of each movement as the angular difference between cursor and target direction 150 ms after movement onset, i.e., before feedback-based corrections could become effective. The median value of this error for each episode and subject was used for subsequent analyses. For further data reduction, we calculated the adaptation indicators

adaptive improvement : $AI\ [°] = 60 - B + A,$ (1)

adaptive retention: $AR\ [°] = 60 - B + R,$ (2)

adaptive transfer : $AT\ [°] = 60 - B + T,$ (3)

de-adaptation: $DA\ [°] = D - B,$ (4)

where B and A represent the mean initial error of the last three baseline and adaptation episodes, whereas R, T, and D represent the initial error of the first retention, transfer and de-adaptation episode. No attempt was made to quantify the amount of savings by comparing the adaptation and retention phases.

As in our previous study (Werner et al. 2008), we quantified subjects' motor performance as the standard deviation of initial errors during the baseline phase (response variability, RV), the coefficient of determination between initial errors and the difference between initial and final errors during the adaptation phase (online correction ability, CA), as well as the mean movement time (MT), reaction time (RT), and peak velocity (PV) across the adaptation phase.

For statistical analysis, we submitted the initial errors of the adaptation phase to analyses of variance (ANOVAs) with the within-factor Episode and the between-factor Group (levels: control / PICA / SCA). To compensate for heterogeneity of variances, we applied Huynh-Feldt-corrections when necessary. In addition we submitted each adaptation indicator and motor performance parameter to a one-factor ANOVA with the between-factor Group. Significant effects of Group were explored with Fisher LSD post-hoc tests.

Again as in our previous study (Werner et al. 2008), we examined the relationship between cerebellar disease, motor performance, and adaptive success by partitioning the variance of each adaptation indicator. To this end we first calculated several multiple linear correlations. R^2_P is the multiple coefficient of determination between adaptation indicator and motor performance measures, R^2_G is the simple coefficient of determination between adaptation indicator and Group (PICA/controls in a first step and SCA/controls in a second step), and R^2_{PG} is the multiple coefficient of determination between adaptation indicator and Group *as well as* motor performance measures. With the help of those coefficients it is possible to calculate the variance that each adaptation indicator shares with motor performance measures (Var_P), with Group (Var_G), and with performance measures and Group jointly (Var_J). These shared variances are given by

$$Var_G = R^2_{PG} - R^2_P, \qquad Var_J = R^2_G + R^2_P - R^2_{PG}, \qquad Var_P = R^2_{PG} - R^2_G, \quad (5)$$

For a more detailed explanation of this method, see, e.g., Bock and Girgenrath (2006).

Imaging data analysis

In the cerebellar patients, a 3D sagittal volume of the entire brain was acquired using a T1-weighted MPRAGE sequence (FOV = 256 mm, number of partitions = 160, voxel size = 1.00 x 1.00 x 1.00 mm^3, TR/TE = 2400/4.38 ms, flip angle = 8 degrees) on a Siemens Sonata 1.5 Tesla MR scanner. Ischemic lesions were manually traced on axial, sagittal and coronal slices of the non-normalized 3D-MRI data set and saved as region of interest (ROI) using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). Spatial normalization into standard proportional stereotaxic Montreal Neurological Institute (MNI) space was performed according to the masking technique described by Brett et al. (2001) using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology, London, UK). Based on the MNI spatial coordinates of cerebellar lesions the corresponding cerebellar lobules were defined with the help of 3D-MRI atlases of the cerebellum (Schmahmann et al. 2000) and the cerebellar nuclei (Dimitrova et al. 2002). Lesions of vermis, paravermis and lateral hemispheres were considered separately (Schoch et al. 2004).

By performing a subtraction analysis (Karnath et al. 2002; Rorden et al. 2007) with the ROIs in MRICroN (http://www.sph.sc.edu/comd/rorden/mricron/) we were able to identify those cerebellar regions related to adaptation data (AI, AR, AT and DA). In a first step right-sided lesions were flipped to the left. Secondly we assorted all patients into one subgroup with impaired AI, AR, AT or DA and one without impairment in AI, AR, AT or DA, respectively. The cut-off value for this classification was the mean value of all control subjects minus one standard deviation. The lesions for the impaired and unimpaired patients were added together, creating traditional overlap images showing the regions of mutual involvement. Thirdly we subtracted the overlap image of the unaffected patients from the impaired groups´ overlap image. This was done for each adaptation variable separately. Our resulting images show regions which are commonly damaged in patients with affected AI, AR, AT or DA.

6.4 Results

Time course of adaptation

Figure 2 shows the mean initial error for each group and episode. During the baseline phase, initial errors were low for control subjects as well as for patients. At the beginning of adaptation phase, initial errors abruptly increased by a similar amount in all groups, and then gradually decrease again throughout the adaptation phase. This decrease was most pronounced and consistent in control subjects, less so in PICA patients, and least in SCA patients. These group differences persisted throughout the remaining experimental phases, except for the convergence of groups at the end of the de-adaptation phase. Initial de-adaptation errors abruptly increase without returning to baseline level within five episodes, thus showing that at least some learning has taken place in all groups.

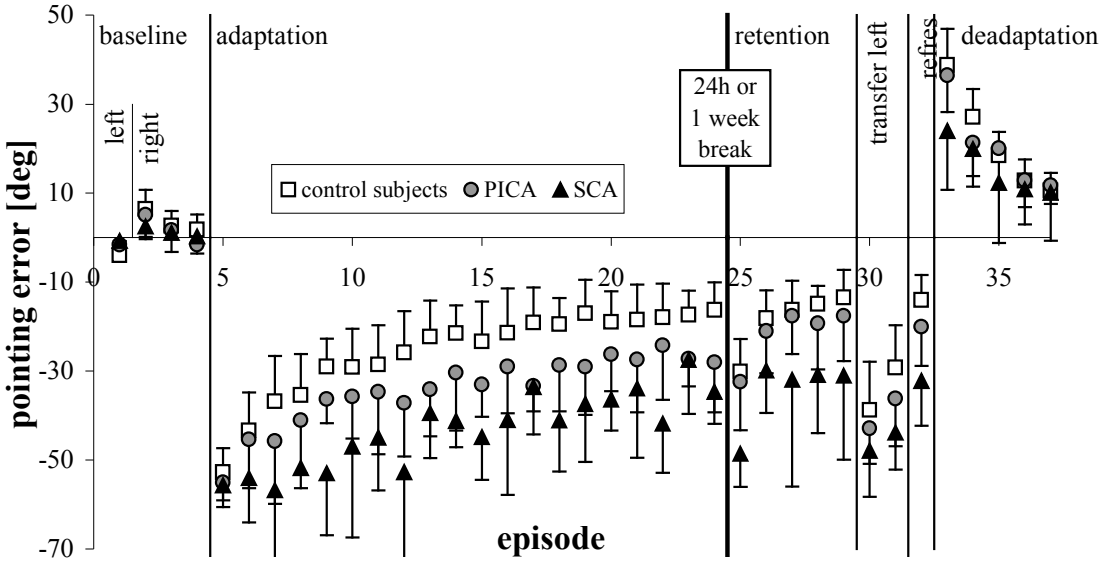

Fig. 2 Initial pointing error for all experimental episodes in SCA patients (*black*), PICA patients (*gray*), and controls (*white*). "Left" or "right" indicate episodes in which subjects used their left or right arm for pointing. *Symbols* represent across-subject means, and *bars* the pertinent standard deviations.

In accordance with these observations, ANOVA of the adaptation phase yielded significant effects of Group ($F(2,29) = 18.38$; $p < 0.001$), Episode ($F(19,551) = 9.50$; $p < 0.001$) and their interaction ($F(19,551) = 18.99$; $p < 0.05$), and post-hoc decomposition revealed significant differences between control subjects and PICA ($p < 0.01$), control subjects and SCA ($p < 0.001$), as well as PICA and SCA ($p < 0.05$). For the retention and transfer phase, ANOVA yielded significant effects of Group ($F(2,29) =$

8.58; $p < 0.01$, and $F(2,29) = 4.55$; $p < 0.05$, respectively), and Episode ($F(4,116) = 3.47$; $p < 0.001$, and $F(1,29) = 12.73$; $p < 0.01$, respectively). Post hoc analysis showed significant differences between controls and SCA ($p < 0.001$), as well as PICA and SCA ($p < 0.01$) during the retention phase, but only between controls and SCA ($p < 0.01$) during the transfer phase. ANOVA for the de-adaptation phase yielded significant effects of Episode ($F(4,116) = 3.37$; $p < 0.001$) and Group × Episode ($F(4,116) = 6.74$; $p < 0.001$), with significant difference between controls and SCA ($p < 0.001$), and PICA and SCA ($p < 0.01$) in the first episode. Furthermore, comparing the last baseline with the first de-adaptation episode reveals significant differences for all groups (controls $t(16) = 15.009$; $p = 0.000$, PICA $t(8) = 10.573$; $p = 0.000$ and SCA $t(5) = -4.149$, $p = 0.009$), thus showing some aftereffect in all subjects.

To explore the role of lesion laterality, we submitted the initial errors of all experimental phases to an ANOVA with the within-factor Episode, and the between-factors Group (PICA/SCA) and Lesion Side (right / left). No significant effects including Lesion Side were yielded. Because all patients were tested with the right hand, one may expect that adaptation was less impaired in patients with left-sided cerebellar lesions compared to right-sided lesions. Ataxia score of the right upper limb however was not significantly different from the left upper limb in SCA ($t(5) = -1.168$; $p = 0.296$) and PICA patients ($t(8) = -1.000$; $p = 0.347$).

Comparison of each adaptation indicator and motor performance parameter for PICA and SCA patients with either right or left sided lesions showed neither significant differences nor any trends. Note that our number of patients is small and a larger sample might lead to different results.

Overall adaptation and performance scores

One-way ANOVAs yielded significant effects of Group for the adaptation indicators AI ($F(2,29) = 12.12$; $p < 0.001$), AR ($F(2,29) = 9.73$; $p < 0.001$), and DA ($F(2,29) = 4.23$; $p < 0.05$), as well as for the performance parameters RT ($F(2,29) = 3.85$; $p < 0.05$), and MT ($F(2,29) = 7.14$; $p < 0.001$). The corresponding means are shown in Figure 3, along with the outcome of post-hoc analyses. For AT ($F(2,29) = 0.95$; $p = 0.40$), CA ($F(2,29) = 1.07$; $p = 0.36$), RV ($F(2,29) = 2.45$; $p = 0.10$), and PV ($F(2,29) = 1.66$; $p = 0.21$), the effect of Group did not reach statistical significance. For the

performance measure RV we found an exceptionally large standard error in SCA patients as also shown in Figure 3. The poorer adaptation as well as motor performance of the SCA group cannot be explained by a larger lesion size, since lesions were actually smaller in that group (SCA: 1.92 ± 1.82 cc; PICA: 14.40 ± 10.28 cc; $t(13) = -2.91$, $p < 0.5$). Nor can it be explained by a larger ataxia, since ataxia scores didn't differ between groups ($t(13) = -1.14$, $p > 0.5$).

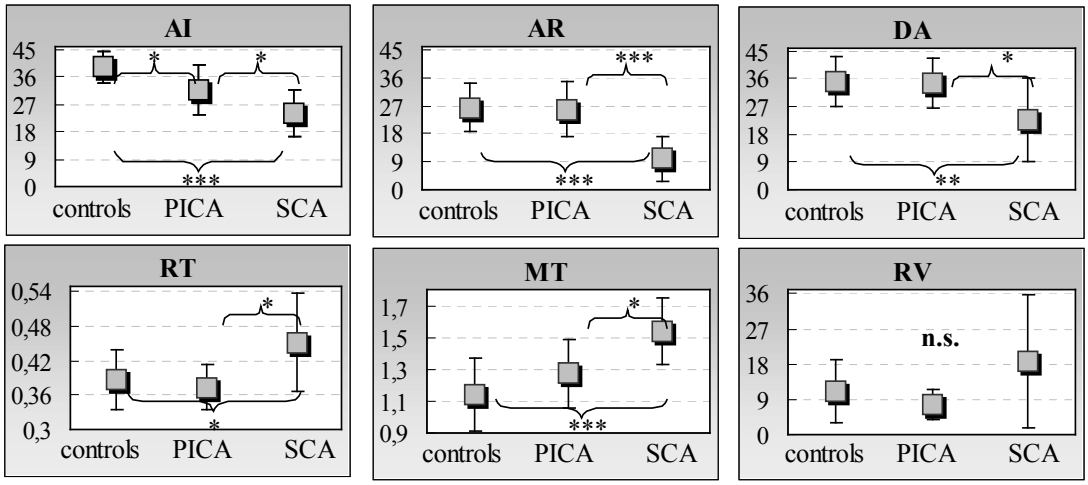

Fig. 3 Mean values and standard deviations for all three groups for AI, AR, DA, RT, MT, and RV. The adaptation indicators were calculated by AI [°] = 60 - B + A, AR [°] = 60 - B + R, AT [°] = 60 - B + T and DA [°] = D - B, where B and A represent the mean initial error of the last three baseline and adaptation episodes, whereas R, T, and D represent the initial error of the first retention, transfer and de-adaptation episode. ***, **, *, and n.s. indicate p<0.001, p<0.01, p<0.05, and p>0.05 respectively. Note that the values of the y-axis stand for pointing errors in ° (AI, AR, DA, RV) or for time in s (RT, MT).

Finding an impairment in AI and DA for SCA patients and in AI but not DA for the PICA patients does not necessarily show, that the pattern is statistically significant for AI and DA measures. Therefore, we performed a further ANOVA with the within-factor Adaptation measure (AI, DA), and the between-factor Group. This analysis yielded a significant effect of Group ($F(2,29) = 7.42$; $p < 0.01$) and a significant interaction Group × Adaptation measure ($F(2,29) = 3.86$; $p < 0.05$). Post hoc analysis showed significant differences between PICA and controls ($p < 0.05$) as well as between SCA and controls ($p < 0.001$) for AI, and between SCA and controls ($p < 0.001$) and between SCA and PICA ($p < 0.01$) but not between PICA and controls ($p > 0.05$) for DA.

One might argue that our results might be confounded by the fact that some of the patients show involvement of interposed (IN) and/or dentate nucleus (DN). However, replicating the one-way ANOVAs with the factor Group (controls/nucleus involve-

ment/no nucleus involvement) or Group (control/DN involvement/no DN involvement) yielded no significant differences between those two patient groups.

Partitioning of variances

When control subjects and PICA patients are considered, the variance of our four adaptation indicators can be partitioned into the components shown in Table 3. Thus, no indicator shares significant variance with Group only, nor with Group and motor parameters jointly, but three indicators share significant variance with motor parameters only. The corresponding analysis for control subjects and SCA patients is found in Table 3. Again, no indicator shares significant variance with Group only, but three share significant variance with Group and motor parameters jointly, as well as with motor parameters only.

PICA	Var_G	Var_J	Var_P	**SCA**	Var_G	Var_J	Var_P
AI	0.096	0.146	0.366***	AI	0.049	0.523***	0.171*
AR	0.001	0.000	0.150	AR	0.021	0.467***	0.197*
AT	0.073	-0.062	0.197*	AT	0.015	0.059	0.137
DA	0.000	0.001	0.232*	DA	0.003	0.254*	0.283**

Tab. 3 Results of multiple linear regression analyses for PICA/controls and SCA/controls. The total variance of each adaptation indicator was partitioned into a component Var_G shared with subject group, but not with motor performance, a component Var_J shared jointly with group *and* motor performance, and a component Var_P shared with motor performance alone. Symbols ***, **, and * indicate $p<0.001$, $p<0.01$, and $p<0.05$, respectively, and the absence of a symbol indicates $p>0.05$.

To determine whether some motor parameters are more important than others, we replicated the analyses in Figure 3, leaving out one motor parameter at a time. It was impossible to exclude any parameter without reducing the number of significant effects, which suggests that all parameters contribute to our results.

Localization of adaptation and motor performance

Figure 4 shows the results of the ROI subtraction analyses for all adaptation variables. The percentage subtraction plots show areas that are more commonly damaged in patients with abnormal AI, AR, AT and DA compared to patients with those variables within the normal range based on control data. The lightest red represents 70%

affected group and darkest blue designates regions where there is an identical percent of affected and unaffected groups (0%). Cerebellar regions with the highest relative percentages of the number of ROIs in the impaired group were analyzed based on MRI coordinates as outlined above.

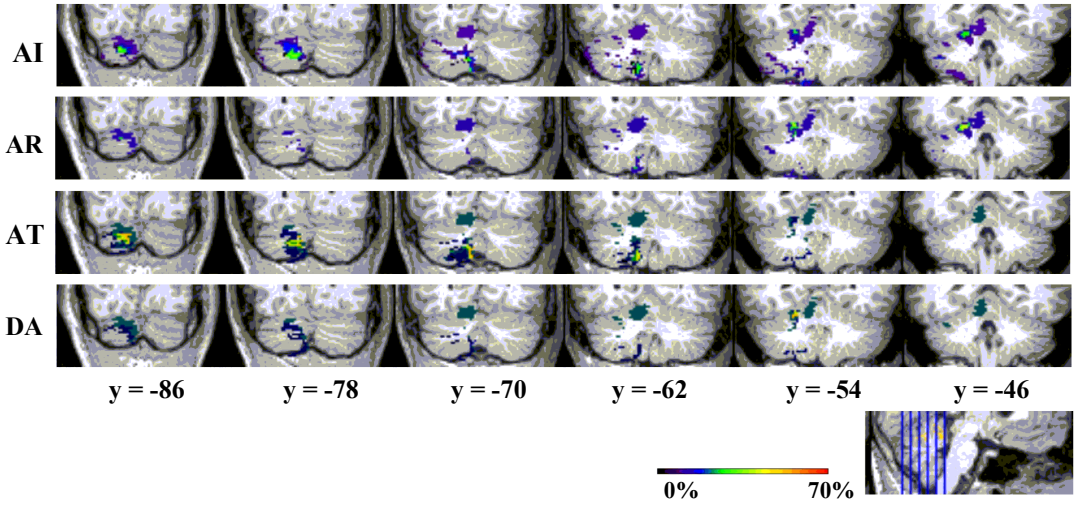

Fig. 4 MRI subtraction analysis comparing lesions in patients with impaired AI, AR, AT, or DA and unimpaired AI, AR, AT, or DA, respectively. The adaptation indicators were calculated by AI [°] = 60 - B + A, AR [°] = 60 - B + R, AT [°] = 60 - B + T and DA [°] = D - B, where B and A represent the mean initial error of the last three baseline and adaptation episodes, whereas R, T, and D represent the initial error of the first retention, transfer and de-adaptation episode. Coronal views are shown (–y = mm behind anterior commissure). The *color* indicates the level of percentage of a region to be more common lesioned in the impaired group.

Subtraction of the sum of the lesions of the subgroup with unimpaired AI from the patients with impaired AI revealed that affection of Crus I (green color; MNI coordinates: x = -18 mm, y = -82 mm , z = -36 mm and x = -18 mm, y = -80 mm , z = -38 mm) was 36% and lobule V (green color; coordinates: x = -20 mm, y = -46 mm, z = -20 mm) was 27% more common in the AI-impaired subgroup (Schmahmann et al. 1999). For AR only affection of lobule V (green color; coordinates: x = -20 mm, y = -46 mm, z = -20 mm) was 38% more common in impaired patients. Furthermore, for the transfer to the other hand Crus II bordering Crus I (yellow color; coordinates: x = -10 to -20 mm, y = -82 to -90 mm, z = -32 to -36 mm) was 50% more commonly affected in the impaired subgroup and for DA lobule VI (yellow color; coordinates: x = -20 mm, y = -56 mm, z = -24 mm) was 50% more commonly affected in DA-impaired patients.

6.5 Discussion

The purpose of the present study was to further elucidate the role of the cerebellum in visuomotor adaptation. We quantified several measures of motor performance as well as of visuomotor adaptation, and found that compared to healthy controls, patients with PICA territory lesions had deficits of adaptive improvement while their adaptive aftereffects and motor performance were not reliably degraded. Our aftereffect tests, adaptive retention and de-adaptation, require newly developed sensory-to-motor transformation rules and thus indicate existing recalibration. Previous studies have shown a dissociation of adaptive improvement and aftereffect measures, for example dependent on age (Bock 2005) or on feedback source (Clower and Boussaoud 2000). Therefore, different underlying processes have been assumed. One might argue that the de-adaptation measure must merely be the difference between the error of the last adaptation episode (with adaptation being achieved by strategic control or recalibration) minus the rotation magnitude (60°). This is true for the first de-adaptation movement. But already in the second movement, the subjects are cognitively aware of the change and must dismiss their previous strategy because it now becomes unsuccessful. Therefore the first de-adaptation episode (about 15 movements) is dominated by recalibration (Clower and Boussaoud 2000; Bock 2005; McNay and Willingham 1998; Redding 1996).

The pattern of our findings therefore suggests that adaptive recalibration remained largely intact in the PICA patients, while strategies like anticipations, associative stimulus-response pairings, and cognitive workaround schemes may be impaired. This would fit well with the observation that subjects with PICA territory lesions have problems on complex (Exner et al. 2004; Kalashnikova et al. 2005; Schmahmann and Sherman 1998) albeit not on simpler (Richter et al. 2007) cognitive tasks.

We further found that patients with SCA territory involvement had even more profound deficits of adaptive improvement, and were additionally impaired on adaptive aftereffects and motor performance. Also, we showed a significant interaction for AI/DA × Group which confirms the assumption of a differentially impaired pattern for SCA and PICA patients. Following again the above line of reasoning, it appears that the SCA group in contrast to the PICA group indeed had deficits of adaptive recalibration. This finding fits well with a previous single-case study which also ob-

served deficient adaptation effects and aftereffects in an SCA patient (Pisella et al. 2005), and with neuro-imaging studies reporting adaptation-dependent neuronal activation in regions commonly supplied by the SCA but not the PICA territory. Furthermore, our findings are consistent with the results of a recent diffusion tensor imaging (DTI) study by Della-Maggiore et al. (2008). Here a positive correlation between the rate of adaptation and cerebellar white matter integrity was found in SCA regions. Also, our results are partly in line with the findings of Martin et al. (1996). Both studies agree that PICA patients show impaired adaptive improvement but intact motor performance. In our study, however, PICA patients were not impaired in measures of aftereffect, therefore, different to Martin et al. our results did not find impairment in true adaptation. Also, for SCA patients Martin et al. found normal adaptive improvement, de-adaptation and motor performance in two subjects, and not measurable adaptation with substantial performance deficits in their third subject. At a more general level, the distinction between SCA- and PICA-related deficits in the present work is compatible with earlier research on other forms of motor learning: SCA but not PICA patients were found to be impaired on different types of eyeblink conditioning (Gerwig et al. 2003; Gerwig et al. 2006; Gerwig et al. 2005).

However, based on the present study alone, it cannot be directly differentiated between effects of strategic change and recalibration. The assumption of a differential contribution of the SCA and PICA territory to strategic change and recalibration needs to be confirmed in future experiments in cerebellar patients including clear manipulations (e.g., see Mazzioni and Krakauer 2006).

Unlike both previous studies with patients with focal lesions (Martin et al. 1996; Pisella et al. 2005), we found no lateralization of the adaptation deficit to the lesioned side. That is, in our study both lesions ipsi- and contralateral to the tested hand appeared to result in deficits in adaptive improvement and recalibration. This is in accordance to imaging data showing activation of bilateral anterior cerebellar regions correlated to the transfer between different angles of rotation (Seidler and Noll 2008), to error correction (Imamizu et al. 2000), and to motor execution (Grafton et al. 2008). In our study, however, no comparison of the lesioned and non-lesioned side was made. Also because of the small sample size, we cannot exclude that deficits are more pronounced on the ipsilesional compared to the contralesional side in a larger group of patients with focal lesions.

To further scrutinize the interrelation between adaptation and motor performance, we determined the variance shared between each adaptation indicator and group only (Var_G), motor performance only (Var_P), and group jointly with motor performance (Var_J). Applying this approach to PICA patients and control subjects, we found that only Var_P, but not Var_G, was significant for most adaptation indicators, suggesting that regions outside of PICA territory are involved in motor performance which correlates with adaptive success. However, applying the same approach to SCA patients and controls revealed significant contributions of Var_J in addition to Var_P to the variances of adaptation variables. This can be interpreted as the involvement of SCA territory *and* extracerebellar brain regions in the monitoring and control of movements which correlates with adaptation. Confirming the outcome of our previous study (Werner et al. 2008), Var_G did not reach statistical significance in either data set, i.e., we found again no evidence for a cerebellar contribution to adaptation but *not* to motor performance. This however, does not say that adaptation disorders are caused by motor performance deficits. Likewise, similar disorders may lead to both disordered adaptation and motor performance abnormalities, or, adaptation deficits may lead to motor performance deficits.

A subtraction analysis of MRI lesion data revealed that regions of the posterior lobe (Crus I) as well as regions of the anterior lobe (lobule V) show common overlap for disordered adaptive improvement. Crus I is commonly supplied by the SCA. However, variation exists and PICA territory can involve Crus I. In fact, in our study, in 7 of 9 PICA patients Crus I was affected, but only in 2 of 6 SCA patients. For visuomotor recalibration, however, lobules V (anterior lobe) and VI (most superior part of the posterior lobe) were the most crucial lesion sites. In line with the results of our subtraction analysis only 3 of 9 PICA patients with Crus I involvement were impaired in AR and 2 of 9 patients in DA. This region of the superior cerebellum has been discussed in numerous imaging studies as important for the processing of performance errors (Diedrichsen et al. 2005; Grafton et al. 2008), for the transfer of adaptation (Seidler and Noll 2008), and as a storage site for internal models (Imamizu et al. 2000). A recent lesion study tested visuomotor adaptation in patients with cerebellar degeneration (Rabe et al. 2009) and found a significant negative correlation between the adaptation deficits and the degree of cerebellar atrophy in the intermediate zone of the posterior lobe. Since their adaptation measure includes aiming errors

during adaptation phase as well as catch trials, it can be compared to both our AI and DA. For those variables we find an involvement of the more intermediate parts of lobules Crus I and VI (which are parts of the cerebellar posterior lobe) and are in accordance with the results in degenerative patients. For the transfer to the other hand subtraction analysis reveals an involvement of a more posterior region (Crus II bordering Crus I). This result indicates that the intermanual transfer might not indicate a deficit in recalibration in cerebellar patients but does require strategic control. Finally, our results cannot be explained by a difference in lesion size in the two patient groups. On the contrary, mean lesion size of our PICA patients was significantly larger than that of our SCA patients. This shows that the exact location of the lesion is more essential than mere size.

The present study as well as previous human cerebellar lesion studies (Deuschl et al. 1996; Gauthier et al. 1979; Maschke et al. 2004; Morton and Bastian 2004; Smith and Shadmehr 2005; Synofzik et al. 2008; Tseng et al. 2007; Weiner et al. 1983; Werner et al. 2008) examined adaptation to sudden visuomotor perturbations. Animal cerebellar lesion studies suggest that abnormalities may be more marked following adaptation to gradual perturbations (Robertson and Miall 1999). It would be of interest to compare adaptation to gradual and sudden perturbation in future studies in cerebellar patients.

In conclusion, the present study confirms the importance of the cerebellum for visuomotor adaptation. While adaptive improvement was impaired in both PICA and SCA patient groups visuomotor recalibration seems to be located within the SCA territory especially lobules V and VI being of particular importance.

6.6 Acknowledgements

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7 Main findings and conclusions

7.1 Theoretical relevance

The present thesis investigates selected behavioral characteristics of sensorimotor adaptation, which is a special form of motor learning. In addition, we tried to clarify the role of the cerebellum in the adaptation process. Both approaches aim at guiding a further understanding of sensorimotor adaptation and its localization within the CNS.

The thesis contains the first experiment ever to directly reveal a *positive effect of explicit knowledge* on sensorimotor adaptation (Study 1). In particular, Study 1 shows that the benefit of explicit knowledge is task-specific and short-lived, and therefore suggests that this benefit relates to strategic control rather than to an adaptive recalibration of the sensorimotor system. This positive effect was also confirmed by Imamizu in a later study (2007), who showed that explicit knowledge reduces movement errors during adaptation to opposing visual distortions and also leads to an overall improved level of adaptation. Furthermore, Heuer and his colleagues not only revealed individual differences of the amount of explicit knowledge to correlate with the degree of adaptation (Heuer and Hegele 2008a), but also found that implicit and explicit processes occur independently and concurrently (Sulzenbruck and Heuer 2009). These results are in accordance with research on serial reaction time tasks (a different form of motor learning), where explicit knowledge also improved learning (Nissen and Bullemer 1987; Reber and Squire 1998; Sakai et al. 2003).

For the identification of the neural correlates of explicit knowledge, results of neuroimaging studies provide detailed information. Whenever explicit sequence learning (as opposed to implicit learning) occurs in a serial reaction time task, brain activation can be detected in the *dorsolateral prefrontal cortex* (BA9, 10 and 46) (Grafton et al. 1995; Jueptner et al. 1997; Sakai et al. 1998; Willingham 1998; Willingham et al. 2002). A further study compared brain activity during explicit sequence learning to activity during adaptation to rotated vision when subjects performed the same motor task (Ghilardi et al. 2000). As a result, activity in the dorsolateral prefrontal and anterior cingulate cortices was associated with explicit learning, while posterior parietal cortex activity was related to visuomotor adaptation. In this context, it must be men-

tioned that the authors state visuomotor adaptation to be a form of implicit learning without determining the subjects' awareness of the distortion.

The above findings together with the results of the first study of the present thesis lead to the assumption that the involvement of the dorsolateral prefrontal cortex in sensorimotor adaptation has a beneficial effect. Moreover, it can be deduced that explicit knowledge plays a role in an early stage of the adaptation process in our study: several imaging studies found early learning to engage prefrontal brain regions (e.g., Clower et al. 1996; Inoue et al. 1997; Sakai et al. 2003; Seidler et al. 2006; Anguera et al. 2007), especially the dorsolateral prefrontal cortex (Anguera et al. 2010).

Another topic of this thesis is the adaptation to left-right reversed vision, where an increase of response variability could be detected for targets along the axis of inversion. Also, a discrete change of the response direction was found for targets perpendicular to that axis and a discrete change followed by a gradual "backward" shift for diagonal targets (Studies 2 and 3). Therefore, the present thesis shows for the first time that adaptation to reversed vision is based on the *same continuous and discrete processes* as adaptation to visual rotations. Until today, numerous studies used adaptation to mirror-reversed vision (Cunningham 1989; Linden et al. 1999; Balslev et al. 2002; Richter et al. 2002; Miyauchi et al. 2004; Caselli et al. 2006; Tanaka et al. 2007; Paquet et al. 2008) and then contextualized their results with findings from adaptation to rotations. By showing that adaptation to left-right reversal and to rotations follow the same basic principles, a comparison of results now becomes possible and acceptable. For example, Paquet et al. (2008) can indeed compare their results of reversal adaptation in patients with Parkinson's disease to those of adaptation to a 90° rotation in the same patient group (Contreras-Vidal and Buch 2003). Similarly, the results of the present studies on adaptation in cerebellar patients (Studies 4 and 5) can be generalized to patients adapting to a visual reversal instead of a rotation.

The finding of Studies 2 and 3 are in accordance with results from a Canadian work group which compared adaptation to 180° rotation and to left-right reversion in patients suffering from either frontal lobe lesions (Richer et al. 1999) or Huntington's disease (Boulet et al. 2005). A careful examination of the statistical analyses of those studies shows that both distortions were learned by the patients in the first study, whereas deficits of the patient group persisted in both distortions in the second study.

Larger deviations during reversal adaptation in both experiments may simply be explained by a different difficulty level of the distortions, and they should be less distinct when comparing adaptation to visual reversal to a (more difficult) 90° rotation.

It can be deduced from the present results that adaptation to those different distortions is based on very *similar neuronal networks*. So far, only one neuro-imaging study tried to directly compare activation during adaptation to visual reversal and to rotation (Moreno-Briseno et al. 2009). For both distortions, brain activity was found in the prefrontal, premotor and posterior parietal cortices as well as in the cerebellum, thalamus and putamen differing only in activation intensity. However, movement errors differed between the distortions and were not adequately controlled. This shortcoming might account for the detected difference in activation intensity and should be carefully considered in future imaging studies.

This thesis further focuses on the question whether visuomotor adaptation is a local or a global phenomenon. A first approach (Study 1) showed that variable practice in all directions does *not lead to faster* rotation adaptation than restricted training in eight directions and does *not have a beneficial effect* on recalibration. Accordingly, this specific condition of practice (namely variable practice) presumably does not lead to a greater generalization or a global adaptation process, respectively. This result is in contrast to the results of Heuer and Hegele (2008b), who showed that one condition of practice (namely the use of terminal visual feedback) could lead to a local adaptation to altered gain, which has been postulated to be a global phenomenon (Bock 1992; Krakauer et al. 2000). Therefore, while global adaptation seems to be a soft constraint in gain adaptation, the present results confirm the notion of local adaptation being a rigid constraint of adaptability in rotation adaptation.

Yet, what is the score on adaptation to (left-right) reversed vision, where in fact different targets require an adaptation to different rotation angles? The findings of the Studies 2 and 3 show that different adaptive processes operate in a *direction-specific fashion*. Several studies had already shown that it is possible to adapt to different visual rotations in separate workspace regions (Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Krakauer et al. 2000). Yet, none of them analyzed the course of adaptation, so the present results are the first to reveal simultaneous discrete and gradual adaptation processes for different target directions, i.e., workspace regions. Furthermore, all of the above mentioned studies used clearly

separated workspace regions, therefore the *overlap* of directionally tuned modules (see also Chapter 1.1.1) could not be scrutinized. Study 3 of the present thesis is the first to analyze adaptation to different rotations in directional proximity. Also, it shows that transfer to unpracticed targets can well be predicted by *superposing neighboring adapted modules*. Transfer to the unpracticed targets, however, was not complete. In contrast, Krakauer (2000) showed complete transfer after adaptation to a 30° rotation with the same number of training targets. This discrepancy seems to oppose the previously postulated comparability of adaptation to visual rotations and reversals. On a more profound level, however, modeling of the overlapping Gaussian tuned processes reveals similar underlying mechanisms for adaptation to both distortions and explicitly shows the benefit of modeling approaches in neuro-physiological research. Conclusively, the results of the present thesis suggest for the first time that adaptation to reversed vision, just like adaptation to visual rotations (Imamizu et al. 1995; Roby-Brami and Burnod 1995; Ghahramani et al. 1996; Pine et al. 1996; Krakauer et al. 2000; Wang and Sainburg 2005), is a local phenomenon based on directionally tuned modules.

A comparison of directionally tuned adaptive modules with similarly tuned neurons can provide insight into where the adaptation process is represented within the CNS. *Directionally tuned neurons*[5] have been identified in primates‘ motor areas of the frontal lobe (Georgopoulos et al. 1982; Amirikian and Georgopoulos 2000), posterior parietal cortex (Andersen et al. 1985; Kalaska et al. 1990) and lobules V and VI of the cerebellum (Coltz et al. 1999). While tuning functions during adaptation to force fields are similar to tuning properties of cerebellar Purkinje cells (Thoroughman and Shadmehr 2000), Krakauer and colleagues (2009) suggest that the Gaussian tuning curves in visuomotor adaptation are best identified with the Gaussian tuned neurons of the parietal cortex (Andersen et al. 1985). In a different study, however, discharge of parietal neurons was modeled with cosine functions (Kalaska et al. 1990). Furthermore, Krakauer‘s assumption is based on the often cited results of Georgopoulos et al. (1982) who originally postulated a cosine tuning function for motor cortex activity, but revised their findings in a more detailed analysis by showing that the tuning width of motor cortex neurons is indeed tuned in the circular normal distribution (von Mises distribution) with a much narrower tuning width than the standard cosine

[5] In directionally tuned neurons, the frequency of discharge varies systematically with the direction of a movement.

tuning function (Amirikian and Georgopoulos 2000). Given these recent findings, the motor cortex might indeed be a potential site for visuomotor adaptation. This notion is further supported by the fact that primate neurons of the motor cortex change their preferred direction of discharge during adaptation to a visuomotor rotation (Paz et al. 2003; Paz and Vaadia 2004a). Conclusively, the results of this thesis suggest that adaptation to visual rotation and reversal are located either in the parietal or in the motor cortex, or in the connections between those two areas.

It can be argued that the adapted neurons are unlikely to represent simple motor command signals and that their population rather reflects the formation of an internal model (Gandolfo et al. 2000). At first glance, this view is supported by the results of Study 3 of this thesis, showing different tuning widths for different rotation angles. However, a detailed analysis of the literature reveals that the widths of neural tuning functions are also variable (Kalaska et al. 1990; Amirikian and Georgopoulos 2000), and that simulated tuned units show different distribution widths after adaptation to different rotations (see Fig. 7 in Tanaka et al. 2009). Furthermore, single-cell recordings revealed that the information content in the activity of directionally tuned neurons improves after adaptation, which again allows an accurate reconstruction of a hand movement direction from neuronal activity (Paz and Vaadia 2004b).

The results of Studies 2 and 3 of the present thesis were achieved by a novel and detailed adaptation data analysis, using *frequency distributions* of adaptation parameters. This method is likely to be very useful in further research on sensorimotor adaptation, since it allows the dissection of the time course of adaptation to different mechanic and visual distortions. For example, Sülzenbrück and Heuer (2009) studied adaptation to a sliding lever, which acts like a tool used in laparoscopic surgery. It causes a complex transformation that is still similar to a visual reversal. They found that subjects adapted to a mirror distortion instead of learning the exact lever transformation. However, without carefully analyzing the time course of adaptation with the help of frequency distributions, it cannot be ruled out that adaptation was not completed and the mirror distortion is therefore only an intermediate step on the (possibly gradual) adaptation process to the lever distortion.

Yet another research focus of this thesis investigates the *role of the cerebellum* in visuomotor adaptation (Studies 4 and 5). The results of both studies suggest that adaptive recalibration is impaired in patients with cerebellar cortical degeneration

(Study 4) and with lesions within the SCA territory (Study 5). By contrast, the outcome indicates that recalibration remains intact in PICA patients, while strategic control is degraded in that very patient group (Study 5). Related to this issue, Taylor et al. (2010) recently exposed patients with cerebellar degeneration to a +45° visual rotation and instructed them to point at the next neighbor of the currently highlighted target to cancel out the effect of the rotation. The patients were able to implement the explicit strategy and, furthermore, their performance remained stable over the course of adaptation (Taylor et al. 2010), while for healthy control subjects pointing errors gradually increase in an overcompensatory fashion (Mazzoni and Krakauer 2006; Taylor et al. 2010). This finding has been interpreted as evidence for the fact that cerebellar pathology selectively disrupts implicit adaptation. However, the result of Study 1 of the present thesis shows the involvement of another (even beneficial) strategy than the one of deliberate past-pointing in visuomotor adaptation, which confirms the notion that impairment in cerebellar patients must not be restricted to implicit adaptation or recalibration, respectively (Study 5).

This thesis clearly demonstrates a *dissociation of impairments* depending on the affected cerebellar area (Study 5). Therefore, results of studies on patients with a cerebellar degeneration should not be interpreted precipitately. It could for example be possible that Taylor et al. (2010) only tested patients who were more affected in superior parts of the cerebellum and therefore did not find any impaired explicit strategy in their patient group. A different study with cerebellar patients shows that the slow process of adaptation is less impaired during adaptive control of saccades, while the fast process or strategic control, respectively, is absent (Xu-Wilson et al. 2009). Following the above line of reasoning (and assuming that the adaptation of pointing movements and of saccades are similarly processed by the cerebellum), it is conceivable that only patients participated in that study who were more affected in posterior inferior parts of the cerebellum. Thus, the present thesis highlights the importance of voxel-based morphometry (Ashburner and Friston 2005; Donchin et al. submitted) or volumetric analysis of MR images (Dimitrova et al. 2006; Brandauer et al. 2008; Rabe et al. 2009) for determining the affected area in patients with cerebellar cortical degeneration.

A further purpose of this thesis is to scrutinize the interrelation between deficits of adaptation and of motor performance in cerebellar patients (Studies 4 and 5). A parti-

tioning-of-variances approach yielded no evidence for the existence of cerebellar circuitry related to adaptation but not to motor performance. These novel results further suggest that cerebellar regions, especially areas of the superior cerebellum (Study 5), and extracerebellar brain regions could be *exclusively* involved in motor performance or could be involved in *both* motor performance and adaptation. It remains an open question whether motor performance is exclusively processed within the cerebellum as a prerequisite of adaptation located elsewhere in the CNS, or whether both functions are processed in identical or highly interlinked cerebellar structures. To definitely answer this question it would be necessary to introduce a task that separates both features. One approach could be telling the patients to use the explicit strategy of past-pointing (Taylor et al. 2010), so that they produce no more movement errors. However, a mismatch remains between observed visual feedback and felt movement, the so called prediction error. This prediction error was reduced by gradually introducing the distortion in a stepwise fashion, yielding contradictory results: On the one hand, cerebellar patients showed degraded gradual as well as sudden *adaptation to a visual rotation*, and impairments did not correlate with severity of ataxia (Klemfuss et al. 2008). On the other hand, only patients with severe ataxia were impaired in sudden but not in gradual *force field adaptation* (Criscimagna-Hemminger et al. 2010). Yet, adaptation to sudden as well as to gradually introduced distortions involve several different movement parameters that are identified by the present thesis to be related to an adaptation deficit. In Study 4, error correction ability, movement time and reaction time were necessary for an explanation of the variability of adaptation indicators, whereas in Study 5, peak velocity and response variability additionally contributed to the correlation. Thus, neither the use of an explicit strategy nor the gradual introduction of the distortion can contribute to a solution of the question. Future work should test cerebellar patients in a setting were their hand is passively moved along a robot-generated and fixed path. This path could then be altered gradually with a cursor that is programmed to always move to the target. This mere *exposure* to a visual distortion has previously been shown to lead to recalibration in healthy subjects (Cressman and Henriques 2010) without producing movement errors, nor noticeable prediction errors, nor volitional movements at all.

Another novel finding of the present thesis is that specific lobules of the cerebellum can be associated with different roles in visuomotor adaptation (Study 5): Lobules V and VI appear to be important for recalibration, whereas lobule V as well as Crus I are the most crucial lesion sites for adaptive improvement. Correspondingly, the region surrounding the primary fissure (lobules V and VI) has been discussed in several imaging studies as key player in sensorimotor adaptation (Imamizu et al. 2000; Diedrichsen et al. 2005; Grafton et al. 2008; Seidler and Noll 2008). Besides, a recent clinical study tested adaptation to visual rotation and to a force field in patients with focal lesions (Donchin et al. submitted) and re-analyzed the data of another group of patients with cerebellar degeneration (Rabe et al. 2009). In accordance to the present results, they found lobule VI to be crucial for adaptation to a visual rotation in both patient groups. Furthermore, lobules IV-V, Crus I and dentate nucleus were related to adaptation in patients with focal lesions, and lobules VIII-X or lobules IV-V, VIIIb-X and Crus I in degenerative patients, depending on the type of analysis. Accordingly, there are some deviations from Study 5 of the present thesis, but they are not consistent throughout patient groups/analyses and might be explained by methodical differences (passively versus actively stopped movements, size of rotation angle, definition of adaptation variables).

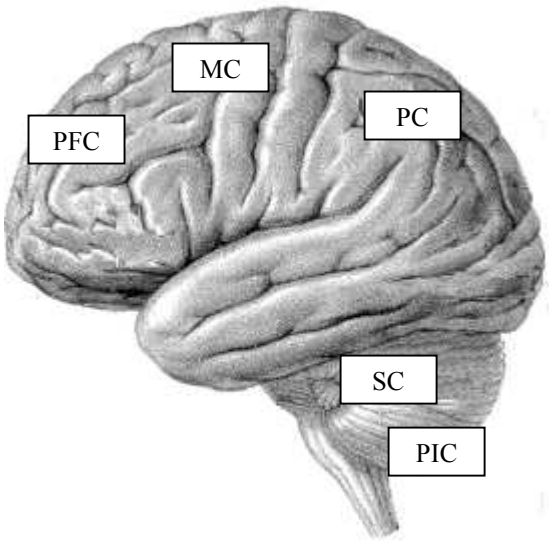

Fig. 2 Lateral view of the brain (modified from Seidler 2010). Brain regions whose involvement in visuomotor adaptation was scrutinized within this thesis: prefrontal cortex (PFC), motor cortex (MC), parietal cortex (PC), superior cerebellum (SC) and posterior inferior cerebellum (PIC).

In summary, this thesis scrutinizes the involvement of several brain regions in visuomotor adaptation. So far, it is commonly accepted that a network of different

brain regions is involved in the adaptation process. Then again, adaptation is a highly selective process that might possibly require only distinct areas of those brain regions, e.g., transforming a distinct population of neurons. The results of this thesis suggest that there can be dorsolateral frontal cortex involvement in adaptation and that this involvement should have a beneficial effect (Study 1). Furthermore, the present results lead to the assumption that either motor areas of the frontal cortex or the posterior parietal cortex can be a possible location for visuomotor adaptation, since both of those brain regions contain adequately directionally tuned neurons (Studies 2 and 3). From the present findings it is also conceivable that adaptation is related to a change in the synaptic weights between those two brain regions. The leading investigation of this thesis scrutinizes the role of the cerebellum in visuomotor adaptation (Studies 4 and 5). No evidence could be found for the cerebellum being exclusively related to adaptation but not to motor performance. Instead the results suggest that the cerebellum can be involved in motor performance alone or in motor performance and adaptation (Study 4). Finally, the thesis demonstrates that areas both within the superior and posterior inferior cerebellum are related to adaptive improvement, but only the superior cerebellum, including lobules V and VI, plays a crucial role in the recalibration of sensory-to-motor transformation rules (Study 5).

7.2 Practical relevance

As the investigations of this thesis have a strong theoretical impact, the thesis rather belongs to the domain of basic research. By revealing important principles of sensorimotor adaptation and by increasing the knowledge of its neuronal correlation, however, these results establish a broad basis for practical applications in sports, daily life and rehabilitation. Still, the transferability of the results needs to be validated in every single case. This drawback is repaid by the fact that a broad range of applications becomes possible once the basic mechanisms are understood.

Results from sensorimotor adaptation studies have the promise of explaining important mechanisms of motor learning or memory in general (Krakauer 2009), because learning of complex motor skills often requires the acquisition of new movements *and* simultaneous adaptation of already learned movements. For example, when children move on from a running wheel to a bicycle, they need to learn to pedal but their

handlebar control only needs to be adapted to a different bike. Also, memory processes do not only play a role during the retention of adaptive processes, but also during other forms of motor learning, for example sequence learning. Shadmehr and Wise (2005) even proposed motor learning to be the sum of motor skill acquisition and sensorimotor adaptation. On the other hand, Krakauer (Krakauer 2010) recently proposed a fundamental difference between sensorimotor adaptation and motor skill learning: the second being reward-dependent, the first one not. In summary, some fundamental similarities can be assumed although the topic remains controversial.

The results of the present thesis lead to several suggestions for the field of sports:

- First, explicit knowledge of changes in the environment should be provided whenever possible (Study 1). For instance, a coach could easily make available explicit knowledge of potential differences between rackets or balls that are used by the athlete. The study did not test whether explicit knowledge needs to be obtained by the athletes themselves, or whether explicit provision by another person would be sufficient. In any case, it is important not to give explicit instructions about *how to handle* the different situation, since this might have a detrimental effect (Mazzoni and Krakauer 2006).
- Second, this thesis could not show a beneficial effect of variable practice for sensorimotor adaptation (Study 1). These findings are in contrast to motor skill acquisition, where this form of practice leads to better performance (Kerr and Booth 1978; Green et al. 1995; Whitacre and Shea 2002). Consequently, the present findings suggest that variable training should not be performed if only sensorimotor adaptation processes are involved; for example during a unit of pole vault training, where different poles are used depending on the height to be cleared.
- Third, this thesis shows that movements are learned in a directionally regional, or rather Gaussian, manner. Therefore, it might be beneficial to train movements in different spatial directions (Study 3). This is done in Aikido, a form of martial arts, where a sword exercise consists of cutting in eight directions. Given the findings of the study, this might indeed lead to a more global sense of one's surroundings or a more global representation of the motor pro-

gram, respectively. Of course, it has to be validated whether directionally learning also holds for the acquisition of complex motor skills.

In daily life, modern technology leads to an increase of workplaces where arm movements are translated into actions on a computer monitor. Here, the investigation of visuomotor adaptation and its location within the CNS does not only have a theoretical impact, but an obvious practical relevance. Certain professional groups encounter very complex distortions between hand movements and the resulting tool actions. For example, an excavator operator has to operate numerous hand gears in order to obtain a desired bucket movement. Moreover, modern medicine has invented highly sophisticated tools, such as levers used in laparoscopic surgery, which are inserted into the abdomen through a small opening. Sliding them to the right or left of their fulcrum in the aperture of the abdomen leads to respective movements to the left or right inside the abdomen. However, sliding them forward or backward within the same plane of movement does not lead to any distortion. Such a tool can therefore be approximated by a simple symmetry operation, or a left-right reversal, respectively. The findings in this thesis (Study 2) help to understand the mechanisms by which such a tool is learned, and it can give implications for the training of surgeons. Namely, explicit knowledge on the exact distortion of such an instrument should lead to faster learning and can therefore reduce the risk for the patients (Study 1).

The most obvious area for practical implications of this thesis is rehabilitation. An increasing number of individuals survive CNS disorders such as strokes, and researchers and clinicians are therefore challenged to develop rehabilitation programs for motor control and learning. Considering the dose of training on stroke rehabilitation, Kwakkel et al. (2004) showed a correlation between intensity of acute and subacute therapy and outcome. Here, basic principles of motor learning as derived from research on healthy subjects or patients with neurological deficits can help deciding on the exact training performance. For instance, it is known that adaptation to a leftward visual deviation improves the symptoms of right hemispatial neglect, a neurological deficit where the left-sided space is completely disregarded by the patient (Rossetti et al. 1998). This effect was shown to last several weeks (Rode et al. 2007). The present thesis further suggests that motor learning should be accompanied by explicit knowledge (Study 1), and that patients should train several movement direc-

tions in order to achieve optimum learning of a task (Study 3, see also Huang and Krakauer 2009).

Adaptation tasks can also be used in rehabilitation to examine whether the CNS' capacity to produce normal movement patterns is retained. For example, adaptation of pointing movements in a force field causes aftereffects which normalize the initial pointing movement of stroke patients (Patton et al. 2006). Accordingly, the results of the present thesis suggest that cerebellar patients might still be able to adapt to a changing environment if their motor performance was trained intensively during rehabilitation (Study 4). Study 5 further implies that different rehabilitation programs should be developed for different cerebellar patient groups, like patients with ischemic lesions within PICA or SCA territory, respectively.

7.3 Critical considerations

Subjects

One critical point of this thesis is the fact that all subjects of the behavioral studies were students of sports science and do therefore not represent the total population. In addition, it is conceivable that their motor experience led to faster adaptation processes. Yet, the pointing movements used in the experiments consist of very simple movements that can easily be performed by any individual. Besides, sensorimotor adaptation occurs on an everyday basis anyways (driving a new car, wearing different shoes, wearing new prescription glasses…), so considerable advantages for sports students are unlikely.

Methods

This thesis tries to specify the location of sensorimotor adaptation within the CNS. However, the presented studies only scrutinize the involvement of four specific brain regions, namely the premotor cortex, motor cortex, parietal cortex and the cerebellum. Although those brain regions were carefully selected (see also Chapter 1.1.2), their exclusive role in adaptation is not automatically implied. Other brain regions, like the basal ganglia or the cingulate motor area, might also be involved. In particular, numerous studies on sensorimotor adaptation in patients with basal ganglia dysfunction found degraded adaptation or impaired aftereffects in Parkinson´s (Stern et

al. 1988; Canavan et al. 1990; Krebs et al. 2001; Contreras-Vidal and Buch 2003; Messier et al. 2007; Paquet et al. 2008; Marinelli et al. 2009) and Huntington´s disease (Paulsen et al. 1993; Boulet et al. 2005) compared to a healthy and age-matched control subjects.

Furthermore, three out of five studies investigated behavioral characteristics that give only indirect information about the neuronal correlates of motor control. One might argue that a more direct and thus better approach is the use of neuro-imaging techniques such as functional magnetic resonance imaging or positron emission tomography. However, several points support our choice of methodical procedure:

- First, the method of drawing conclusions about neural correlates from the results of behavioral studies is widely used and accepted within the scientific community (e.g., Wolpert et al. 1995; Krakauer et al. 2000; Schmitz et al. 2010).
- Second, imaging techniques are not without drawbacks either (see also Chapter 1.1.2). They show brain activity of the holistic state of the scanned human being, including emotions, cognitive functions or movements. Also, statistical analyzes have to be conducted very precisely in order to avoid false positive activation prediction, as spectacularly shown in a study reporting brain activity in a dead fish (Bennett et al. 2009).
- Thirdly, scanners are very expensive and not widely available.

In Studies 4 and 5, cerebellar patients performed our experiments assuming that adaptation deficits indicate the contribution of the respective brain region to the performed task. However, one should bear in mind that the observed behavior reflects the effect not only of the lesion itself but also of connected brain regions which might be disturbed by the lesion. Furthermore, it might also be possible that the patient adjusted to the lesion and is now using a completely different brain subsystem.

One limitation of the present results is the fact that only adaptation to visual distortions was investigated. It remains unclear whether the present results can be generalized to sensorimotor adaptation (e.g., adaptation to force fields), motor learning or neural plasticity in general. However, the chosen methods are prototypical for sensorimotor adaptation research. By showing that adaptation to visual rotation and reversion follows the same basic principles, the present thesis indeed adds to the possi-

bility to generalize results. As previously discussed (Chapter 7.2), some fundamental similarities between sensorimotor adaptation and motor learning in general can be assumed. Also, since neural plasticity depends on neural activity and can be induced by training (Leonard 1998), sensorimotor adaptation indeed triggers this very process. Thus, adaptation research has the promise of revealing basic principles of plastic changes within the adult brain.

Individual studies

In Study 1, two aftereffect tests for measuring recalibration were conducted. One of them (persistence without visual feedback) was shown to improve after the development of explicit knowledge. Yet, the results were explained as if explicit knowledge had no effect on recalibration. This interpretation can be justified by the fact that the subjects had been instructed to continue performing their pointing movements *as before*. Thus, those subjects who had developed explicit knowledge might have explicitly used it during the persistence phase. In further studies different instructions should be given.

In Studies 2 and 3, we found simultaneous discrete and gradual adaptation. It is conceivable that these findings are merely due to the use of a special target set with two targets each on the axis of reversal and on the orthogonal axis. Accordingly, target axis effects, i.e., different aiming errors depending on target direction, were found during adaptation (Cunningham and Pavel 1991; Caselli et al. 2006) as well as under non-transformed movements (Keele 1968). However, the aim of the present studies was to show that discrete and gradual adaptive processes *can* occur simultaneously and targets-specific manner. Adaptation to visual reversal with eight uniformly distributed targets with omitting the previously used axes has recently been investigated in our laboratory and revealed discrete processes for all directions (preliminary data).

Concededly, Study 4 would have yielded additional insights if a volumetric analysis of MR images of the cerebellar patients had been performed to determine the affected areas. Still, this study provides novel findings of defining the role of the cerebellum in sensorimotor adaptation. Furthermore, the study on patients with focal cerebellar lesions (Study 5) promised to give even more insight into exact localisation of adaptation. One drawback of Study 5 is that laterality effects were only partly investigated. Approximately one half of the patients in each group had left hemi-

sphere lesions, while the other half had right hemisphere lesions. However, all patients were right handed and performed the task with their dominant hand. In this study, both lesions ipsi- and contralateral to the tested hand led to adaptation deficits, but a larger sample size might have revealed a more pronounced deficit on the ipsilesional side. Also, the results might have been clearer if all patients had been tested with the arm ipsilateral to their cerebellar lesion, which is commonly done (Martin et al. 1996; Pisella et al. 2005; Donchin et al. submitted).

7.4 Outlook

The present novel findings raise numerous research questions that could be explored in future work. For instance, further research could scrutinize whether adaptation to mechanical and visual distortions follows similar processes. On the one hand, this thesis reveals a beneficial effect of explicit knowledge on visuomotor adaptation and it would be interesting to find out whether the same holds for adaptation to force fields. On the other hand, the present results suggest that adaptation to left-right reversal and to rotations are based on directionally tuned modules. In particular, Study 3 suggests different tuning widths for different rotation angles. From this finding it can be speculated that differences between narrow tuning widths in adaptation to visual rotations and broad tuning widths in force field adaptation might not be discrete but gradual. Future work could investigate this notion.

In addition, it remains to be determined whether the results from the present behavioral studies can be transferred to different age groups, i.e., adaptation in children or in the elderly. Pertinent to this issue, adaptation to reversed vision has recently been investigated in our laboratory and, in contrast to the present results, showed it to be based only on discrete processes (Thomas et al. 2009).

A further remaining question concerns the involvement of the cerebellum in motor performance as a prerequisite of adaptation or its simultaneous involvement in adaptation per se. Apart from the previously mentioned task paradigm, where cerebellar patients would merely be exposed to a gradually introduced distortion (see also Chapter 7.1), it is also conceivable to conduct a carefully controlled imaging study to answer this question. Indeed, such a study has already been conducted in our laboratory and is currently being analyzed.

Last but not least, this thesis suggests an involvement of prefrontal cortex, motor cortex, parietal cortex and the cerebellum in sensorimotor adaptation. The functional connections between those different brain regions should be explored in future work.

8 Summary

The present thesis investigates behavioral characteristics of sensorimotor adaptation and its neural localization. This special form of motor learning occurs whenever an altered environment requires the adjustment of already existing motor behavior. Sensorimotor adaptation does not only play a dominant role in everyday life, but it is also an intrinsic element in the field of sports. For instance, tennis players have to adjust their movements to rackets, balls or field conditions. In the following, the main results of the individual studies of this thesis as well as their implications are summarized.

To this day, it is not entirely clear whether explicit knowledge has a beneficial or a detrimental effect on sensorimotor adaptation. This thesis therefore tries to determine the role of explicit knowledge in sensorimotor adaptation, and is the first to reveal a *positive effect of explicit knowledge on adaptation*. In particular, our results lead to the assumption that the positive effect is related to strategic control. Furthermore, they suggest that an involvement of the dorsolateral prefrontal cortex leads to improved sensorimotor adaptation.

Furthermore, the present thesis scrutinizes whether adaptation to different alterations of feedback is based on common principles. It compares the adaptive processes caused by a rotation and a reversal of visual feedback, and it shows for the first time that *adaptation to reversed vision is based on the same continuous and discrete processes as adaptation to visual rotations*. According to this finding, similar neuronal networks for both adaptive processes can be assumed.

The thesis also investigates whether adaptation to a change of visual feedback is a directionally local or a global phenomenon. We show that *variable practice in all directions does not lead to an improved adaptation to a visual rotation*, which is thought to be achieved by directionally tuned modules. Accordingly, variable practice does presumably not induce a greater generalization or a global adaptation process, respectively. Also, we show *direction-specific adaptive processes during adaptation to reversed vision*. Moreover, *transfer to unpracticed targets* could well be predicted by the superposition of neighboring adapted modules. These results lead to

the conclusion that adaptation to reversed visual feedback is based on a local process. This finding is associated with the involvement of Gaussian tuned neural units in sensorimotor adaptation.

Finally, this thesis scrutinizes the contribution of the cerebellum to sensorimotor adaptation by investigating adaptation processes and motor performance in two cerebellar patient groups. In particular, we investigate whether different parts of the cerebellum play different roles during adaptation. The results suggest that *adaptive recalibration is impaired in patients with cerebellar cortical degeneration* as well as *in patients with lesions within the territory of the superior cerebellar artery*. The findings further indicate *an intact recalibration but degraded strategic control in patients with lesions within the territory of the posterior inferior cerebellar artery*. A partitioning-of-variances analysis supports the suggestion that (superior) cerebellar regions are exclusively involved in motor performance or are involved in both motor performance and adaptation.

9 Zusammenfassung

Die sensomotorische Adaptation ist eine spezielle Form des motorischen Lernens, die immer dann auftritt, wenn veränderte Umweltbedingungen die Anpassung eines bereits bestehenden motorischen Verhaltens erfordern. Sie spielt sowohl bei Alltagshandlungen als auch im Bereich des Sports eine wichtige Rolle. Die vorliegende Arbeit befasste sich mit Verhaltensmerkmalen der Adaptation und ihrer neuronalen Lokalisation.

Ein Experiment konnte erstmals einen positiven Effekt von explizitem Wissen auf die sensomotorische Adaptation belegen. Aus diesem Ergebnis folgt die Annahme, dass eine Beteiligung des dorsolateralen präfrontalen Kortex zu einer verbesserten Adaptation führen kann. In einem weiteren Experiment wurde die Adaptation an unterschiedliche Veränderungen des visuellen Feedbacks untersucht. Da für verschiedene Adaptationen die gleichen kontinuierlichen und diskreten Prozesse gezeigt werden konnten, liegen ihnen möglicherweise ähnliche neuronale Netzwerke zugrunde. Diese Arbeit zeigte zudem, dass die Adaptation bei bestimmten Veränderungen des visuellen Feedbacks richtungsabhängig erfolgt. Dieses Resultat deutet auf die Beteiligung des motorischen oder des parietalen Kortex hin, da beide Hirnareale Neuronen aufweisen, die in ähnlicher Weise richtungsabhängig kodiert sind.

Außerdem untersuchte diese Arbeit die Rolle des Kleinhirns in der sensomotorischen Adaptation. Zwei Experimente ergaben, dass Patienten mit degenerativen Erkrankung des Kleinhirns und Patienten mit Läsionen im Gebiet der oberen Kleinhirnschlagader sowohl eine Verminderung der Adaptation als auch eine Beeinträchtigung der motorischen Durchführung zeigen. Diese Ergebnisse lassen vermuten, dass entweder die motorische Durchführung im Kleinhirn lokalisiert und eine Voraussetzung für die Adaptation ist, die an einer anderen Stelle im zentralen Nervensystem stattfindet. Oder es ist möglich, dass sowohl die motorische Durchführung als auch die sensomotorische Adaptation im Kleinhirn lokalisiert sind.

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