The Neural Control of Anticipatory Postural Adjustments during Bimanual Movements

by

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Abstract

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When we use two hands to manipulate an object, each hand must anticipate the consequences of the actions of the other hand. These anticipatory postural adjustments (APAs) were studied in both normal and neurologically impaired populations. In the first study, patients with cerebellar lesions due to either bilateral degeneration or focal unilateral insult and one callosotomy patient were tested in a task in which one hand lifts an object held in the other hand. The normal APA for this task involves a reduction in the upward force generated by the postural arm just prior to the object being lifted. This APA minimizes an upward perturbation of the postural hand. The results indicate that, while the APA was not reduced in size, the adaptive timing was deficient in the patients with cerebellar lesions. Furthermore, the size of the APA was not modulated by prior experience. In contrast, the APA in the callosotomy patient was unimpaired. In the second study, healthy college-age students were tested on various conditions in which the unloading was triggered by either an arbitrary action (button press) or by a predictive external visual or somatosensory event. The APA was only learned in the button-press condition, suggesting that a prerequisite for learning the unloading APA is an efference copy from a voluntary action. The involvement of the cerebellum and the corpus callosum in the acquisition of the APA was investigated in the third study. Patients with cerebellar damage were unable to associate an APA with a button press, providing the first empirical evidence that the cerebellum is necessary for the acquisition of intermanual coordination. In contrast, learning was observed in the split-brain patient. A neural model is proposed for the generation and acquisition of postural responses during bimanual actions.

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Chapter 1

Introduction

1.1 Anticipatory motor behaviors

How does the brain produce movements? The naive answer to this question goes like this: The primary motor cortex represents each body part in the form of a somatotopic map (Penfield & Jaspers, 1954). If we want to raise our arm, neurons in the arm area become active; if we want to wiggle our toes, the neurons in the toe area become active. This theoretical picture implies that there is a set of labeled lines from central structure to peripheral muscles. The brain moves the body like a puppeteer moves a puppet on a string.

The shortcoming of this simple conception should become immediately clear to anybody who actually has tried to move a marionette. If one tries to produce an arm movement just by pulling on the appropriate string, the arm does indeed go up. However, the rest of the puppet is also perturbed. This creates the impression that the movement is caused by an external agent. The skillful puppeteer prevents this perturbation by compensatory measures and induces the impression that the movement is caused by the volition of the puppet itself.

The perturbations we observe when we move a single limb of the puppet are similar to those that would occur in people should they move each limb individually. Static and dynamic consequences of actions must be considered. After the movement, the body will be in a new position and its center of gravity will be shifted. During the movement, the force that accelerates the limb has a corresponding counter-force in the opposite direction acting on the supportive joint, giving rise to what are called interaction torques. If these consequences of the movement are not accounted for, postural instability of the body and possibly the failure of the movement will result.

To prevent the perturbations caused by voluntary movements, the central nervous system exhibits a repertoire of anticipatory postural adjustments (APAs). APAs accompany the activity of the main acting muscle for a given action in the same manner that instruments in an orchestra accompany a soloist. Thus, the coordination or synergy between movement and posture is an important feature of action and must have a central place in the neuroscience of movement (Bernstein, 1967).

1.2 Three general characteristics of anticipatory postural adjustments

One of the general characteristics of APAs is their *anticipatory* nature. While a range of spinal and supra-spinal reflexes work to promote postural stability of the body against unexpected perturbations, the time lag inherent in these feedback driven processes can allow perturbations to become large and require subsequent, effortful corrections. Thus, the change of activity in postural muscles has to precede activity in the prime movers. For example, when rapidly lifting the arm, the tibialis anterior (ankle flexors) contracts prior to the onset of the deltoid muscle. In this manner, the induced interaction torque caused by the raising of the arm is neutralized with a forward shift of the body (Bouisset & Zattara, 1987; Diener, Dichgans, Guschlbauer, Bacher, & Langenbach, 1989; Nougier, Teasdale, Bard, & Fleury, 1999).

Furthermore APAs are *adjustable* to the characteristics of the action. More rapid actions produce larger dynamic perturbations. Accordingly, the size of the APA must be scaled with the velocity and size of the focal action (Horak, Esselman, Anderson, & Lynch, 1984; Lum, Reinkensmeyer, Lehman, Li, & Stark, 1992). However, the perturbation also depends on the environment and the objects with which the body interacts. For example, when lifting an object, the initial load and grip forces and the activity in the postural muscles are scaled to the expected weight of the object, often based on past experiences (Flanagan, King, Wolpert, & Johansson, 2001; Forssberg, Jucaite, & Hadders-Algra, 1999; Gordon, Westling, Cole, & Johansson, 1993; Wing, Flanagan, & Richardson, 1997). In a similar manner, when catching a falling object, the anticipatory increase in the activity of the arm flexors depends on the expected kinetic energy at impact, a function of the drop height and the mass of the object (Lacquaniti & Maioli, 1989b; Morton, Lang, & Bastian, 2001; Shiratori & Latash, 2001). APAs are also modified according to the overall postural state of the person. For example, when one hand is used to provide postural support, even by just a light touch against a stable surface, the size of a postural APA is reduced (Aruin, Forrest, & Latash, 1998). Thus, the brain uses many sources of information to predict the state of the body and the world and adjusts the behavior accordingly. These processes occur effortlessly and typically outside consciousness. Only in situations where our expectations are violated do we become aware of them, for example when lifting a nearly empty milk-carton in the expectancy to find it full.

Finally, many aspects of APAs seem to be *acquired* through learning. While feedback-driven mechanisms are present with the development of movement (Massion, 1998), feed-forward control emerges much later in life (Forssberg et al., 1992; Hay & Redon, 1999, 2001; Schmitz, Martin, & Assaiante, 2002). Children as young as two years show some anticipation of the weight of an object during the initial phase of the lift; however, they do not acquire the fully adult-like patterns until the age of eight (Eliasson et al., 1995).

1.3 APAs in the context of bimanual actions

In many situations, we hold an object with one hand while manipulating it with the other. Skilled bimanual performance demands a tight coordination of the two hands. When opening a jar, the holding hand increases the grip force in anticipation of the force that the other hand will apply to remove the lid (e.g. Scholz & Latash, 1998; Witney, Goodbody, & Wolpert, 2000). In the bimanual context, the physical interactions between the two limbs depend on the object that is being manipulated, rather than being caused by a fixed linkage as in the case of interactions that arise between the elbow and shoulder joints during arm-movements. Thus, APAs in the bimanual context require an accurate prediction based on an internal model not only of the body, but also of the environment (Miall & Wolpert, 1996). As such, hardwired coordinative structures between the hands would be of little help.

Much of the research on bimanual coordination has focused on stereotyped coordination tendencies that become apparent when the two hands perform different tasks (rubbing one's head while patting one's stomach). However, many of these phenomena may instead reflect general limitations that arise when we do two things at once rather than tell us anything interesting about bimanual coordination (Diedrichsen, Hazeltine, Kennerley, & Ivry, 2001; Diedrichsen, Ivry, Hazeltine, Kennerley, & Cohen, 2003; Hazeltine, Diedrichsen, Kennerley, & Ivry, 2003; for a review see Ivry, Diedrichsen, Spencer, Hazeline, & Semjen, in press; Mechsner, Kerzel, Knoblich, & Prinz, 2001).

A task that captures bimanual coordination in a stricter sense was introduced by Massion and colleagues (Hugon, Massion, & Wiesendanger, 1982; Massion, Ioffe, Schmitz, Viallet, & Gantcheva, 1999; Paulignan, Dufosse, Hugon, & Massion, 1989). In this task, an object is held in one hand. The other hand is then used to lift the object. The postural hand shows an anticipatory lowering of flexor muscle activity just prior to the lift. This APA is functionally useful in that it reduces the resulting upward perturbation. If the load is lifted by the experimenter, no APA is visible and the perturbation of the hand is much larger (Dufossae, Hugon, & Massion, 1985).

1.4 One single process or two interacting processes?

Two views about the relationship between volitional actions and their accompanying APAs have been proposed (Aruin & Latash, 1995; Slijper, Latash, & Mordkoff, 2002; Slijper, Latash, Rao, & Aruin, 2002). According to a two-process model (Massion, 1984), the APA is produced by a separate control structure. To implement APAs constrained by the timing and scaling of a focal action, this system would need to receive information from the control structure implementing the action. Outside of this input, the APA controller is considered independent of the controller associated with the volitional action. In contrast, a single-process view would hold that the APA is an integral part of the action and controlled in tight conjunction with it.

These two models make opposite predictions concerning four aspects of the relationship between action and APA. First, the two-process view allows for the possibility that APAs may be triggered in the absence of a voluntary action, e.g. by sensory information predictive of a perturbation, whereas the one-process view would be inconsistent with this notion. Evidence suggests that for most behaviors an externally triggered perturbation, even when predictable to the subjects, does not lead to anticipatory postural adjustments (Blakemore, Goodbody, & Wolpert, 1998; Dufossae et al., 1985; Struppler, Gerilovsky, & Jakob, 1993; Witney, Goodbody, & Wolpert, 1999). In contrast, when catching a falling object, visual information predictive time of impact is sufficient to elicit an appropriately scaled APA (Lacquaniti & Maioli, 1989a, 1989b; Shiratori & Latash, 2001). To reinvestigate this issue in the context of the bimanual unloading task, I test in Chapter 2 (Diedrichsen, Verstynen, Hon, Lehman, & Ivry, 2003) whether extended practice with different kinds of sensory information that provide better temporal information might lead to learning of an APA. The experiment confirms, however, that a voluntary action is necessary for eliciting an APA, providing evidence for a one-process model.

Second, a two-process model would imply that once-learned, APAs can be linked to any arbitrary eliciting action, whereas a one-process model would predict that the APA will preferably be linked to actions that naturally cause that perturbation. In favor of a two-process view, it has been shown that participants learn to exhibit an APA in the unloading task after medium amounts of training (60-100 trials), even when the triggering action is relatively arbitrary, such as popping a balloon (Aruin & Latash, 1995) or pressing a button (Paulignan et al., 1989).

Third, if the APA and action are controlled together, then the APA may vary with characteristics of the action, even if these are irrelevant to the resultant perturbation. Indeed, smaller actions usually lead to a reduction in the size of the accompanying APA, even though the resultant perturbations might be identical those elicited by larger action (Aruin & Latash, 1995; Paulignan et al., 1989; Slijper, Latash, & Mordkoff, 2002). This indicates that the linkage between the volitional action and APA cannot be completely arbitrary.

Finally, the relationship between APA and action should be fixed under the one-process model, whereas the two-process model would allow many other variables to intervene and modulate the APA for a given action. Congruent with latter view the linkage between action and APA changes with the task circumstances. For example, the relative timing of the APA depends on the preparatory time associated with an action. Changes in postural muscles precede the focal action by a larger amount when the participant initiates the action in self-paced manner compared to when a speeded response is required (Nougier et al., 1999; Slijper, Latash, & Mordkoff, 2002). It is also evident that APAs can be rapidly modified by experience. Whitney et al. (2000) used a task in which the volitional action consisted of pulling one end of a object while holding it with the other hand. The behavior of the holding hand depended strongly on the preceding few trials. Only when the object had been experienced as consisting of one part was an anticipatory increase in grip force observed. Thus, the same action elicited very different APAs in these two situations.

Whereas experiences made while interacting with the environment are incorporated very quickly into APAs, symbolic visual information seems much less effective. Horak, Diener, and colleagues studied postural adjustments when people stood on a platform that could produce various perturbations. The magnitude of the postural response rapidly became matched to the amplitude of the perturbation when the latter was held constant over a few trials (Horak, Diener, & Nashner, 1989). However, completely predictive visual precues failed to elicit any modulation of the response (Diener, Horak, Stelmach, Guschlbauer, & Dichgans, 1991). This favors a one-process view in which in the APA and the action form an encapsulated unit that is shielded from the rest of the cognitive system. This contrasts with the accessibility of cognitive information to APAs in other situations. For example, when lifting objects, visual information and long-term memory representations certainly play a role in programming grip forces and postural adjustments (Gordon et al., 1993; Wing et al., 1997).

In sum, the present data indicate partial, but not complete independence of the controllers associated with the volitional action and APA. The role of sensory information in shaping the APA appears to be restricted to perturbations that are intimately linked to objects, i.e., those during lifting or catching.

1.5 Neural implementation

What neural structures are responsible for the production of APAs? Lesions encompassing the motor cortex contralateral to the postural arm extinguish production and learning of the APA in the unloading task (Massion et al., 1999; Viallet, Massion, Massarino, & Khalil, 1992; see also Slijper, Latash, Rao et al., 2002; Bennis, Roby-Brami, Dufosse, & Bussel, 1996). This impairment is not due to the inability to innervate the musculature of the arm, because the patients in these studies had recovered other motor functions at the time of testing. Additionally, Gauthier et al. (1992) found heightened APAs in the unimpaired leg when patients moved their paretic leg. The postural control center appeared to be unimpaired. The APA was even larger than required, likely caused by the fact that the outgoing motor command to the paretic limb had to be strengthened to overcome the muscular weakness, inducing a APA proportional to the perceived effort rather than to the actual resulting movement. These data indicate, consistent with the two-process model, that the motor cortex contralateral to the postural hand is part of the system producing APAs. The data indicating the involvement of other cortical motor structures, such as the supplementary motor area (SMA), are in comparison rather weak (Viallet et al., 1992).

Although both motor cortices are involved in the bimanual load lifting task, one in the production of the voluntary action and the other in the APA, this aspect of bimanual coordination is not disrupted by resection of the corpus callosum (Viallet et al., 1992). This is somewhat surprising, given that callosotomy abolishes many forms of bimanual coupling (Diedrichsen, Hazeltine, Nurss, & Ivry, under review; Franz, Eliassen, Ivry, & Gazzaniga, 1996; Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002). However, it is important again to differentiate between tasks in which the two hands work to achieve a common goal and tasks in which the hands attempt to produce independent actions. Interference between independent bimanual movements appears to reflect callosally-mediated interactions, likely involving abstract spatial codes represented in cortical areas (Ivry et al., in press). In contrast, the coordination of the two hands producing one action may be mediated by subcortical mechanisms. This conjecture is congruent with the observation that split-brain patients still can tie their shoes effortlessly (Franz, Waldie, & Smith, 2000).

At present, little is known about the contribution of different neural structures associated with the hypothesized subcortical network for anticipatory postural control (Massion et al., 1999). One proposed site for the generation of APAs is the basal ganglia (Franz et al., 2000; Massion et al., 1999). Congruent with this hypothesis, patients with Parkinson's disease show some impairments in the generation and learning of APAs (Massion et al., 1999; Viallet et al., 1992). However, other authors report little or no deficit (Dick et al., 1986; Diener et al., 1989; Gordon, Ingvarsson, & Forssberg, 1997). The discrepancy may relate to slowness of the voluntary actions in these patients, making it hard to measure the APA reliably (see Chapter 2). In sum, there seems to be agreement that APA-related deficits in Parkinson's disease are quantitative rather than qualitative (Aruin, Neyman, Nicholas, & Latash, 1996).

While alternative subcortical sites, including the spinal cord, the red nucleus and the reticular formation have been implicated in postural control (e.g. Prentice & Drew, 2001), some experimental work and considerable theoretical conjecture has focused on the role of the cerebellum. Microstimulation of the dentate nucleus in the baboon elicits stereotypical patterns of muscular activity across multiple joints (Rispal-Padel, Cicirata, & Pons, 1981, 1982), similar to muscle synergies required for postural stabilization during movement. Patients with cerebellar lesions show poorly timed stance-related APAs prior to volitional actions (Diener et al., 1989). Moreover, when the amplitude of the perturbations is manipulated, cerebellar patients fail to show adjustments in the postural response based on recent experience (Horak & Diener, 1994). This learning-related deficit is not manifest as a complete inability to generate predictions or to modify APAs based on these predictions, but rather as the failure to do so fast and efficiently (Lang & Bastian, 1999, 2001; Timmann & Horak, 1997).

1.6 Overview of the studies

Somewhat surprisingly, no studies have examined the effects of cerebellar lesions on postural adjustments associated with bimanual coordination. The experiment reported in Chapter 2 addresses this problem. Two groups of patients with cerebellar lesions were tested on the basic bimanual unloading task in which one hand is used to lift an object held by the other hand. One group of patients had bilateral cerebellar degeneration; the other group consisted of patients with unilateral lesions due to stroke or tumor. The results indicate that while, the APA was not reduced in size, both the adaptive timing (Diener et al., 1989) and the responsiveness to prior experiences (Horak & Diener, 1994) were abnormal. One split-brain patient was also tested in the study and provides a replication of the finding that resection of the corpus callosum does not disrupt the coordination between the hands in this task, a pivotal observation that was previously based on a single patient (Viallet et al., 1992).

In Chapter 3, I compare the acquisition of APAs when the unloading is triggered by a volitional, yet arbitrary action (i.e., a button press) to conditions in which the unloading is external, but preceded by a highly predictive sensory event. The results indicate that the APA is not acquired even after extended practice when the eliciting event does not involve a volitional action. Thus, the nervous system requires an efference copy in order to learn an APA during unloading.

In Chapter 4, I explore the role of the cerebellum and the corpus callosum in the learning task in which unloading is triggered by an arbitrary action. Patients with cerebellar damage fail to learn the APA, providing the first empirical evidence that the cerebellum is necessary to acquire a new coordination between the hands. In contrast, the split-brain patient showed preserved learning abilities. Based on these results a refined neural model for the generation and acquisition of postural responses during bimanual tasks is proposed.

Chapter 2

Neural structures involved in the production of APAs during natural unloading

2.1 Abstract

A callosotomy patient and a group of patients with bilateral cerebellar degeneration or unilateral cerebellar lesions were tested in a bimanual load-lifting experiment. The hand that supports an object shows a reduction of force in the anticipation of the unloading, and the rapidity of this response scales with the size of the expected perturbation. The response was found to be unimpaired in the split brain patient. This confirms the hypothesis that the coordination between the two hands is achieved via subcortical structures. While cerebellar patients also showed intact size and scaling of this anticipatory postural adjustment (APA), they showed an earlier onset of the response. Furthermore, in contrast to healthy controls, the APA was not modulated by recent experiences of unexpected perturbations. This indicates a role of the cerebellum in the adaptive timing of this behavior and in the rapid modification in response to changes in the environment.

2.2 Introduction

In order to produce coordinated action, the central nervous system must integrate movements across different parts of the body. For example, we often hold an object with one hand and manipulate it with the other. This creates a physical linkage between the hands that makes it necessary for each hand to anticipate and account for forces generated by the other hand. A popular experimental paradigm to study anticipatory postural adjustments (APAs) in bimanual actions is the unloading task, pioneered by Massion and colleagues (Hugon, Massion, & Wiesendanger, 1982; Massion, Ioffe, Schmitz, Viallet, & Gantcheva, 1999). In this task, participants hold an object in one hand. When the object is lifted off the hand by the experimenter, the hand shows a rapid upward perturbation (Dufossae, Hugon, & Massion, 1985). However, when the person picks up the object with their other hand, the upward perturbation is greatly attenuated. This attenuation is due to an anticipatory reduction of the force produced by the load-bearing muscles of the postural arm that can be observed just before the load starts being lifted (Hugon et al., 1982).

How does the brain accomplish the integration of movements across limbs that are controlled by different cerebral hemispheres? The first and somewhat surprising finding is that interhemispheric communication across the corpus callosum does not seem to be necessary for the APA in the unloading task. A patient with complete resection of the corpus callosum showed evidence of normal anticipatory lowering of the force in the postural arm prior to unloading (Viallet, Massion, Massarino, & Khalil, 1992).

One possibility is that the hemisphere contralateral to the active hand causes both the voluntary action of unloading and the APA of the postural hand. The APA may be generated via ipsilateral descending pathways or inhibitory spinal interneurons (Figure 2.1a). This hypothesis is at odds with the finding that the contralateral hemisphere to the postural hand plays a major role in the production of this behavior. Anticipatory adjustments are extinguished in hemiparetic patients with damage involving the corticospinal tract innervating the postural hand (Bennis, Roby-Brami, Dufosse, & Bussel, 1996; Massion et al., 1999; Viallet et al., 1992). Furthermore, damage to the SMA contralateral to the postural hand reduces the size of the APA (Viallet et al., 1992).

These findings have led to the alternative hypothesis of a subcortical anticipatory network (Massion et al., 1999) that receives an efference copy from the acting hand. It in turn either generates the APA directly via descending fibers or transmits the signal to the contralateral hemisphere, which then is involved in generating the APA (Figure 2.1b).

The empirical support for the subcortical hypothesis is quite thin and much remains to be explored. First, the critical observation that the APA is preserved after callosotomy rests on an experiment involving one individual, a situation that demands replication. Second, the exact nature of the proposed subcortical anticipatory network is unknown. Massion (1999) suggested the cerebellum as a possible site, a conjecture that is consistent with the hypothesized role of this structure in multi-joint coordination (Bastian, Martin, Keating, & Thach, 1996; Thach, Goodkin, & Keating, 1992). However, the involvement of this structure in the unloading task has not been tested.

An important methodological issue in investigations of intermanual coordination during unloading is the fact that the size of the APA is intimately linked to the size of the expected perturbation, which in turn is a function of the speed at which the unloading action is performed (Lum, Reinkensmeyer, Lehman, Li, & Stark, 1992). This relationship has been largely ignored in previous neurological studies of the unloading task. For example, Viallet et al. (1987) found a smaller EMG change prior to unloading in Parkinson patients. The

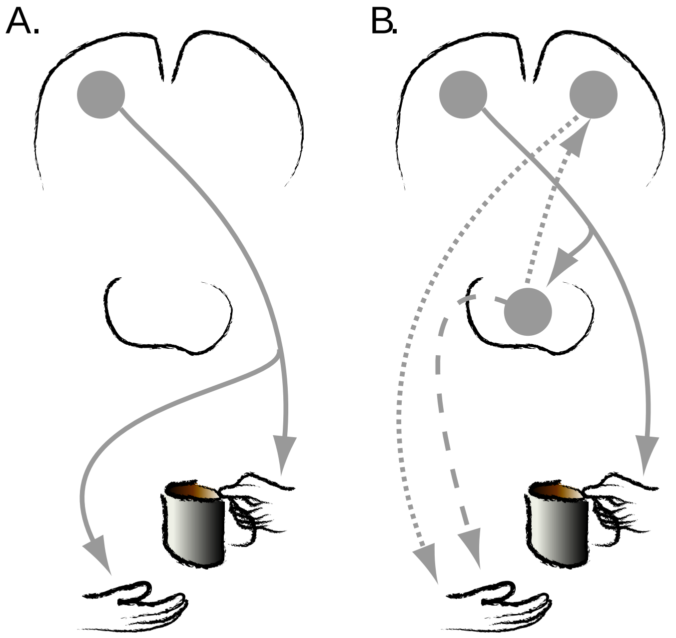

Figure 2.1: *Two neural hypotheses concerning the generation of the anticipatory postural adjustment in the unloading task. (A) Single-hemisphere hypothesis: the hemisphere contralateral to the unloading hand controls both the volitional lifting movement and the postural adjustment, with the latter dependent on ipsilateral cortico-spinal projection or spinal interneurons. (B) Subcortical-locus hypothesis: An efference copy of the signal to the unloading hand is sent to a subcortical locus (e.g cerebellum), which in turn generates the APA, either via descending fibers (dashed line) or in conjunction with the contralateral cortical hemisphere (dotted line).*

patients, however, also performed the unloading action substantially slower than controls. Thus, the reduction in the APA may have been due to their slower movements, rather than a disruption of bimanual coordination.

In this study, a patient that had undergone callosotomy, patients with cerebellar lesions, and age-matched control participants were tested on the unloading task. The participants were encouraged to vary the speed of unloading action to allow an explicit assessment of the relationship between the APA and the action of the unloading hand. In this manner, it should be possible to determine whether changes in the APA truly reflect an impairment in bimanual coordination.

2.3 Method

2.3.1 Participants

Seven patients with bilateral cerebellar degeneration, seven patients with unilateral cerebellar lesions and eleven age-matched control participants were tested (Table 2.1, Table 2.2). Ataxia ratings were obtained for all cerebellar patients using the International Cooperative Ataxia Rating Scale (Trouillas et al., 1997). This scale provides an assessment of postural and gait disturbances, limb ataxia, dysarthria and oculomotor disorders. Other neurological disorders or indications of dementia, as assessed by a standard neuropsychological battery, served as exclusion criteria for this study. Approval for the project was granted by the Committee for the Protection of Human Subjects at UC Berkeley.

Table 2.1: *Participant demographic information: Gen: Gender, YoE: years of formal education, H: Handedness.*

	Gen	Age	YoE	H
Bilateral cerebellar degeneration group				
JH	M	63	20	R
AG	M	37	16	R
OH	M	54	15	R
LB	F	56	18	R
AW	M	76	12	R
JF	M	67	17	R
MF	M	51	18	R
Mean		57.7	16.5	
Unilateral cerebellar lesion group				
CB	M	53	13	R
JD	M	58	12	R
JV	M	57	11	L
MN	M	47	18	L
TR	M	76	18	R
EC	M	66	14	R
SL	M	45	18	L
Mean		58.2	14.4	
Control group				
Mean	6F/5M	57.2	15.5	1L/11R

Table 2.2: *Patient information: Ataxia rating according to the international cooperative ataxia rating scale. PO: Posture, LL, LR: Limb ataxia left and right, SP: speech disorders, OM: Oculomotor disorders. maximal impairment score in parenthesis. YsO: years since onset of symptoms or since insult. Aet.: Aetiology. SCA = spinocerebellar ataxia genetic subtype AT = atrophy of unknown origin, Loc: Location. LH, RH: left or right cerebellar hemisphere, lobules in Larsell-notation. D: Dentate Nucleus*

	Ataxia Rating					Lesion Description	
	PO (34)	LL (24)	LR (24)	SP (8)	OM (6)	YsO	Aet./Loc.
Bilateral cerebellar degeneration group							
JH	4	4	4	3	3	5	AT
AG	12	10	10	3	2	13	SCA2
OH	7	3	3	3	5	12	AT
LB	11	6	6	4	2	4	AT
AW	20	8	9	5	2	42	SCA6
JF	13	11	9	6	3	41	SCA3
MF	18	12	12	3	4	13	SCA3
Mean	12	7.7	7.4	3.9	2.8	18.5	
Unilateral cerebellar lesion group							
CB	2	7	0	2	0	7	LH: I-VIIb
JD	8	6	1	1	4	12	LH: VIII, IX
JV	8	7	1	5	3	6	LH: I-IX, D.
MN	11	0	13	4	4	6	RH: VI-VIII
TR	1	1	1	1	0	11	RH: I-VIIb, D.
EC	13	0	10	2	0	12	RH: I-V, VI
SL	3	0	11	1	4	3	RH: I-IX, D.
Mean	6.3	8	0	2.1	2	8.1	

2.3.2 Apparatus and stimuli

The experiment was performed in a virtual-reality environment. Participants viewed a 22' monitor at a distance of 46 cm through a mirror positioned 10 cm below their eyes. A realistic 3d-image of the environment was displayed that showed a workspace measuring 40 cm in width, 35 cm in depth, and 26 cm in height and viewed at a distance of 65 cm in an oblique angle from above. An object that consisted of a 20 x 10 x 2 cm handle, sitting on top of a 4 x 4 x 7 cm foot was presented in this workspace.

The haptic experiences or the combined aspects of touch and proprioception, arising from the interaction with this workspace were simulated by two robotic arms (Phantom 3.0, Sensable Technologies). An accurate physical model of the workspace was maintained in the computer and updated at 1000 Hz. At each of the update cycles, the computer measured the positions of the hands and calculated the forces acting on the object. The surface was simulated as a dampened spring model (2.5 N/m), with lateral frictional components. The object had a virtual weight of 0.5 kg and could only be moved in the vertical direction, but could not rotate or tip. Summing the forces acting on the object, the computer calculated the acceleration of the object, updated its position, and finally computed the resultant forces to the hands according to the same surface model. These forces were then applied to the hands via torque motors, thus closing the loop. The haptic feedback was calibrated to match the visual stimulus and the result of this simulation was the convincing impression of an interaction with a real object.

Participants wore a splint on each hand that was attached to the phantom device. The splint immobilized wrist and finger joints throughout the whole experiment. Movements of the upper limbs were restricted to the elbow joint in order to allow for the computation of the torque generated at this joint via inverse dynamics.

2.3.3 Measurement of APA

The assessment of the APA and its scaling relationship with the voluntary action from kinematic data is a non-trivial problem, given that the physical link between the hands needs to be considered. In particular, the perturbation of the postural hand will vary as a function of the speed at which the object is lifted. If the unloading action is performed more rapidly, the force on the postural hand will decrease more rapidly and the resulting perturbation will be larger.

Two complementary approaches will be used to address this issue. First, "trick" trials are used to break the physical link between the actions of the two hands. On these trials, the participant is provided with the same haptic and visual feedback when the unloading arm moves to lift the object. The force on the postural arm, however, is held constant despite changes in the object's position. A lowering of the force in the postural arm in anticipation of unloading should lead to a downward deflection of the hand. Trick trials thus provide an uncontaminated assessment of the feed-forward command (Diedrichsen, Verstynen, Hon, Lehman, & Ivry, 2003; Lum et al., 1992). However, because trick trials quickly change the behavior of the participants (see Thoroughman & Shadmehr, 2000), the number of these trials has to be restricted.

Second, the forces generated by the postural arm on normal trials can be inferred from the kinematics of the arm, while accounting for the impending forces. This approach involves inverse dynamics and will be described in detail below.

2.3.4 Procedure

To start a trial, participants lifted the object with either the left or right hand to a visually specified height, 3-6 cm above the floor of the workspace, and held it in this region for 2 s. On external-unloading trials the computer initiated the unloading at an unpredictable time point thereafter. The computer simulated the upward force acting on the object to mimic force generated by the unloading hand during natural unloading (see Figure 2.2b). The movement of the object and forces on the postural hand were computed to provide the realistic impression of a moving object. The object was unloaded at three different speeds that differed noticeably from each other. The subjects were informed of the forthcoming speed on external-unloading trials by the presentation of the word "slow", "medium" or "fast".

On self-unloading trials, the unloading hand was positioned approximately 3 cm below the object's handle. A lateral force field helped to maintain the hand in the correct position. When the unloading hand remained stable for 2 s and did not touch the object, an auditory starting signal was played. Participants were instructed to lift the object with the unloading hand in one smooth motion, without stopping when the hand first touched the object. The trial ended when the object had reached a height of 12 cm above the floor of the workspace. Feedback about the speed of the unloading action, from the moment the unloading hand touched the object until the end of the trial, was given. Participants were instructed to unload the object at a range of speeds, approximately matching those of an external-unloading condition. The object had to be placed back on the floor to start the next trial.

The experiment began with eight practice trials in the external unloading condition and sixteen practice trials in the self-unloading condition, eight with each hand. This was followed by 10 test blocks run in the order of two external, four self-unloading, two external and finally, four self-unloading blocks. The postural hand alternated between blocks and the starting hand was counterbalanced between subjects. Each block consisted of 24 trials, from which six were randomly selected to be trick trials. On trick trials, the visual feedback and the force feedback to the unloading hand were identical to normal trials. However, the force applied to the postural hand on these trials was held constant at the gravitational force of the object, 4.9 N (Figure 2.2a,c, dotted lines).

2.3.5 Inverse dynamics

Figure 2.3 depicts the forces involved in the unloading task. In the example shown, the participant holds the object with the left hand by producing an adequate torque at the elbow joint. This torque translates to the internally generated force (F_{in}) at the connection point between object and phantom device (called pivot point in the following). For simplicity, all further analyses will be based on the forces at the pivot point, rather than joint

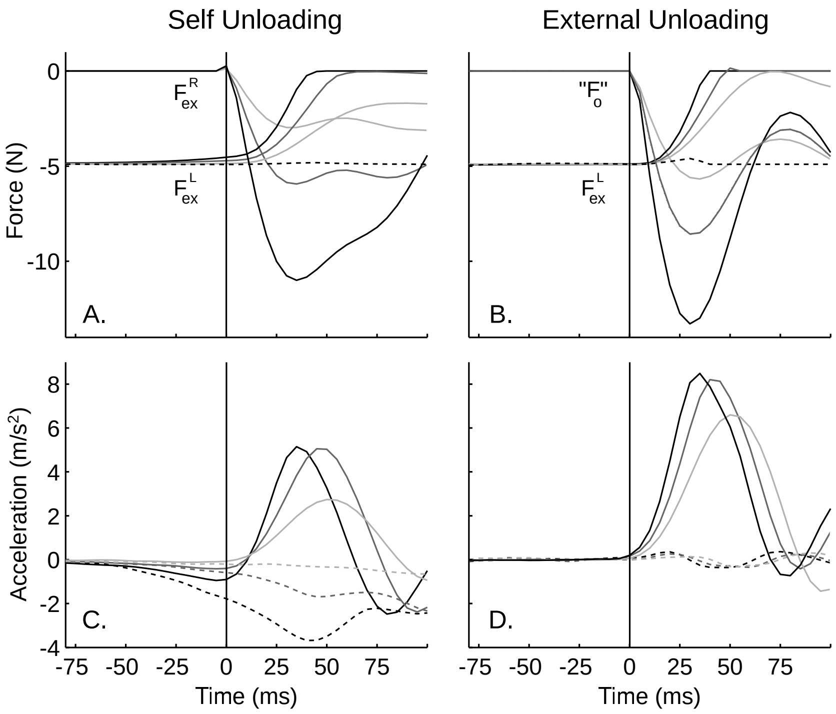

Figure 2.2: *Data from one control participant, with the left hand used as the postural hand. A. Average force traces during self unloading. The external force applied to left hand (*F_{ex}^{L}*, caused by holding the object), and the force applied to the unloading hand (*F_{ex}^{R}*, caused by lifting the object) are both negative to indicate their downward direction. Traces are aligned to the beginning of the unloading (0ms). B. In external trials the computer "lifts" the object, simulated by creating an upward force against the object (*F_O*), also shown as negative values for comparison purposes. Panels C and D show average acceleration traces of the left hand, again aligned to the start of the unloading. The data is split into fast (black), medium (medium gray) and slow (light gray) trials, depending on the size of the self-produced or external force impulse. Force and acceleration traces for trick trials, in which the force against the postural hand is held constant, are shown in dotted lines.*

torques. Because the position of the hands varies only over $\sim$ 5 cm, corresponding to an approximately 6 deg change in elbow angle, the relation between the torque at the elbow joint and the internal force at the pivot point is approximately linear. The gravitational force on the hand and forearm (F_g) is considered to be a constant within the small range of motion, and will be subsumed into the internal force. The external forces arising from the interactions of the object and the actions of the other hand (F_{ex}) are simulated by the phantom device. These forces, along with the position of the object, x_O, the left hand, x_L, and the right handx_R were sampled at 200 Hz.

The APA corresponds to a change in forces generated by the elbow of the postural

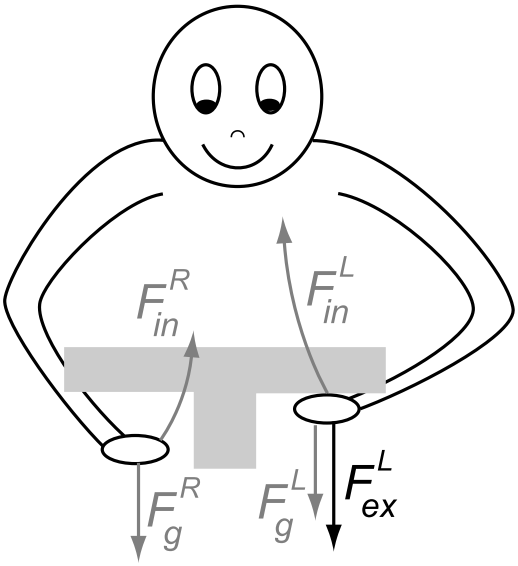

Figure 2.3: *Forces involved during unloading. The left hand holds the object. The torque generated at the elbow joint leads to an upward internal force (F_{in}^{L}) at the pivot point. This force resists the gravitational force acting on the forearm and hand (F_{g}^{L}) and the force exerted by the object (F_{ex}^{L}), which is simulated by the phantom device. The right hand does not touch the object, so that no external forces are applied to that hand.*

arm. To determine these forces from the recorded external forces and the acceleration of the hand, I used an inverse dynamics approach. Specifically, the force acting on the postural hand is linearly related to the acceleration ($\ddot{x}$) and velocity ($\dot{x}$) of the hand.

$$F_{in} = -F_{ex} - F_g + v\dot{x} + m\ddot{x} \tag{2.1}$$

The viscosity v of the elbow joint is likely rather low and hard to measure reliably (Latash & Gottlieb, 1991). Because the resultant velocity of the postural hand during the first 45 ms of the unloading was approximately 0.1 m/s for external unloading and even smaller in the self-unloading condition, the term likely plays only a minor role and will be ignored. Finally an estimate of the inertia of the hand, m, is needed. This value likely depends on the position and load of the elbow joint. Furthermore, the phantom device itself has a considerable internal inertia, likely dependent on load and direction of movement (see Appendix B). The data from the external-unloading condition can be used to estimate m. Since the exact time of unloading in this condition is not predictable for the subject, the internal force should remain constant until the body can react to the perturbation. While mono-synaptic spinal reflexes can lead to measurable EMG activity as fast as 25 ms after a perturbation, measurable forces due to spinal reflexes are typically not apparent until after 50 ms. Thus, until this time, the relation between the external force and acceleration of the hand should be linear with a slope of $1/m$. Moreover, the slope should be independent of unloading speed. Both the linearity and constant slope predictions were confirmed (Figure 2.4). The same estimate of m was then used in the self and external-unloading conditions.

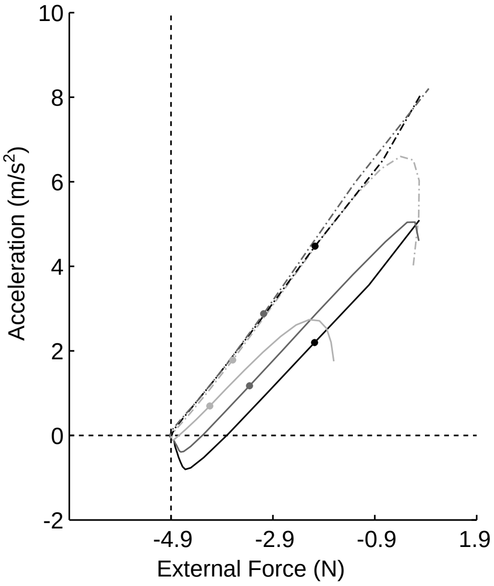

Figure 2.4: *Relationship between external force (F^L_{ex}, shown in Figure 2.2a,b) and acceleration (Figure 2.2c,d). Data are from one control participant in which the left hand was used as the postural hand during external unloading trials (dashed) and self-unloading trials (solid). Dots indicate values at 30 ms after the beginning of unloading. Fast (black), medium (dark gray) and slow (light gray) trials are shown separately. Dotted lines indicate the force/acceleration when the hand holds the object stationary.*

2.4 Results

2.4.1 Force traces & initial impulse

The development of the forces acting on the hands can be seen in Figure 2.2a,b. The size of the initial impulse to the object (the integral of the force applied by the unloading hand over the first 45 ms) served as a measure of the speed of the unloading action. The data in the self-unloading condition were split by the size of this measure into three categories with equal numbers of observations for each hand: fast, medium and slow unloading.

The control participant whose data are depicted in Figure 2.2 was not successful in performing self-unloading over the same range of speeds as used in the external unloading condition. For each third of the data, the impulse of self-unloading was lower than for the corresponding external unloading speed condition. This pattern was observed for both

Table 2.3: *Initial impulses (Ns) over the first 45 ms upon impacting the object. External pulses were applied at three speed (fast, medium and slow), whereas the data from the self-unloading condition was divided in three categories based on the initial impulse. Data for unilateral patients is shown separately for trials in which the ipsi- or contralesional hand held the object.*

	Fast		Medium		Slow	
	Mean	SD	Mean	SD	Mean	SD
External condition	0.45		0.29		0.19	
Control group	0.31	0.071	0.19	0.045	0.10	0.035
Bilateral cerbellar	0.40	0.060	0.25	0.049	0.14	0.052
Unilateral ipsil.	0.34	0.065	0.24	0.054	0.14	0.030
Unilateral contral.	0.32	0.074	0.21	0.056	0.11	0.050
Callosotomy patient	0.31		0.25		0.17	

control and cerebellar groups (Table 2.3). Nonetheless, all participants did generate a range of speeds during self-unloading, which allows the assessment of the relation between unloading action and APA, so that differences caused by different unloading speeds can be taken into consideration. The bilateral cerebellar patients applied a slightly higher initial impulse to the object, $F(1, 16) = 7.11$, $p = .017$, while the unilateral patients did not differ significantly from the control group, $F(1, 16) = 1.89$, $p = .188$. While the unilateral patients found it harder to unload the object with their ataxic hand (Table 2.3, row 5), no significant difference in initial impulse was found between ipsi- and contralesional hands, $F(1, 6) = 3.13$, $p = .127$. The considerable spread of unloading speeds and the rather large differences between individuals has to be taken into account when interpreting the size of the APA.

2.4.2 Estimation of inertia

Principal component analysis (PCA) was used to obtain an unbiased estimate of the slope of the line for the first 30 ms after the start of the unloading action for each individual external-unloading trial[1]. The resulting estimate for the inertia of the hand/phantom system averaged across all participants and sides was 0.61 kg for the slow condition and 0.59 kg for both the medium and fast conditions. The within-arm standard deviations for the slow, medium, and fast conditions were 0.046, 0.035 and 0.031 kg, respectively, indicating that the estimates for the slow condition were more variable than for the other two conditions.

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[1] As both force and acceleration are measured with noise, a regression analysis would result in a systematic underestimation of the true slope, and a corresponding overestimation of the inertia (Berkson, 1950). PCA finds the axis of maximal variability, and the orientation of the axis indicates the slope (see Figure 2.4).

I thus considered only the estimates from the medium and fast conditions. There was no significant difference between the estimates for these two speeds, $t(24) = 1.64$, $p = .11$. The inertia estimate for the combined unilateral and bilateral cerebellar patients groups were higher on average than the control group, $t(23) = 1.64$, $p = .587$, very likely related to the higher bodyweight in the patient group compared to the control group. For the unilateral cerebellar group, no difference was found between the ipsilesional and contralesional limb, $t(6) < 1$. The correlation between the inertia estimate for the left and the right arm was .68.

2.4.3 Internal forces calculated by inverse dynamics

Based on the measured external force and acceleration of the postural hand, Equation 2.1 was used to compute the internal force of the postural hand, using the estimated inertia for that limb (Figure 2.4). Prior to unloading, the internal force was always 4.9 N, the force required to resist the load of the object. In the external unloading condition (Figure 2.5a), this force remained constant until around 50 ms after the start of the unloading. At this time, spinal and functional (cortical) stretch reflexes caused a drop in force in the postural limb and counteracted the upward acceleration.

A very different picture was observed in the self-unloading condition (see Figure 2.5b). Starting 50-60 ms before the start of the unloading, the force generated by the elbow joint of the postural hand began to decrease, leading to a slight downward deflection. This decrease was identical for normal and trick trials until 50 ms after the start of the unloading when stretch reflexes lead to a divergence of the two curves. The fact that the lines for the normal and trick trials are identical is important methodologically: Despite very different impending forces and resultant accelerations, the estimate of the internal force by inverse dynamics converges to the same value during the initial phase of the trial. The small artifact in the fast condition at 40 ms was related to the rapid force transient caused by the detachment of the object from the hand.

Figure 2.5c presents the results from one patient with bilateral cerebellar degeneration. Similar to the controls, this patient showed a clear reduction of the forces in the postural arm prior to unloading and a scaling of the APA to the anticipated speed of the unloading action. The reduction of applied force, however, began much earlier than in the control participants. In the next section I will explore these effects in a quantitative fashion. For this analysis a measure of the size and onset of the APA that accounts for differences in the speed of the unloading action is needed.

2.4.4 Size and scaling of the APA

On self-unloading trials, the APA manifests as a decrease in the internal force generated by the postural hand prior to the unloading of the object. The APA was clearly related

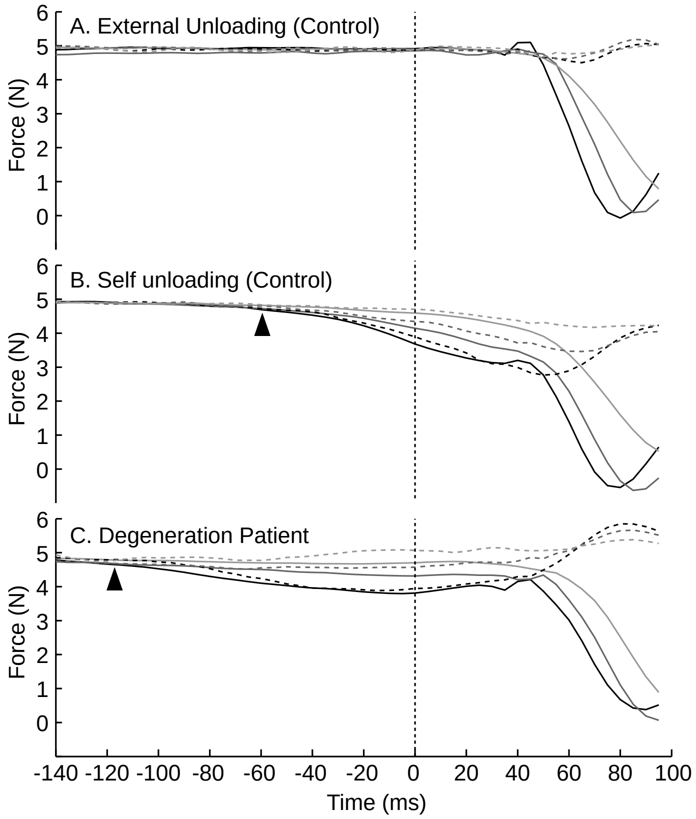

Figure 2.5: *Estimated internal force in the postural hand (F_{in}) calculated for (A) external-unloading trials, and (B) self-unloading trials, both for the postural right hand of one control participant, and (C) for the self-unloading trials for a patient with bilateral cerebellar atrophy. The data is split according to the speed of the unloading movement: fast (black), medium (dark gray) and slow (light gray). For the self-unloading trials, the division into these three categories is based on the initial impulse of the unloading hand as described in section 2.4. The onset of the APA is marked with a triangle.*

to the size of the forthcoming initial impulse produced by the unloading hand (Figure 2.5b,c). When the size of the initial impulse caused by the unloading hand is plotted against the average internal force (0-45 ms) of the postural hand for each trial, a strong linear relationship is apparent (Figure 2.6). To compare the size of the APAs between participants and hands, an estimate of the APA that accounts for this relationship in needed. For this purpose, I used the slope of the regression line between the impulse and average internal force over the time window from 0 to 45 ms. The intercept of this regression was held constant at 4.9 N, as the unloading hand would not show an APA if the unloading action were executed indefinitely slowly. Because regression without an intercept is highly

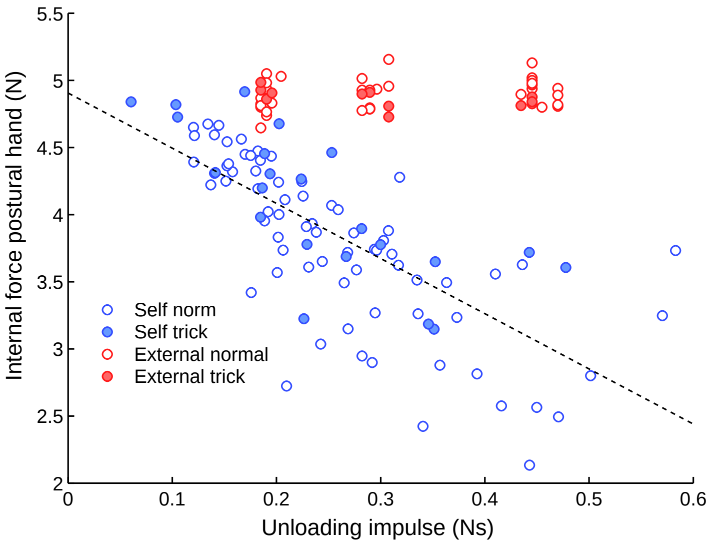

Figure 2.6: *The internal force generated by the postural arm is related to the speed of a forthcoming unloading movement. The unloading impulse is the integral of the force applied to the object by the unloading hand (or on external trials, the simulated force) over the first 45 ms. The internal force of the postural hand is averaged over the same time-window. The regression line (with a constant intercept of 4.9 N) for the self-unloading trials was calculated by pooling trick trials (solid blue) and normal trials (empty blue). For comparison, the values for the external-unloading trials are shown in red.*

susceptible to outliers, robust regression was used for the estimation of slopes[2].

The regression coefficients provide a measure of the size of the anticipatory postural adjustments. As shown in Figure 2.7, the mean size of the APAs was similar for the controls and the cerebellar patients. To compare the bilateral cerebellar patients with the control group, I performed a repeated-measures ANOVA with hand (dominant vs. non-dominant) as a within-subject variable and group as a between-subject variable. Neither the effects of group, $F(1, 15) < 1$, nor hand, $F(1, 15) < 1$, nor the Hand x Group interaction, $F(1, 15) < 1$, were significant. Three planned comparisons were performed for the unilateral cerebellar patients: The within-subject contrast between ipsi- and contralesional hands, was not significant, $t(6) = 1.58$, $p = .16$. I also tested the between-subject contrast of ipsilesional hand vs. control performance, and contralesional hand vs. control performance. Because the lesion affected the dominant hand in three and the non-dominant hand in four patients,

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[2] Robust regression (Huber, 1981) was performed using an iteratively reweighted least-squares procedure, in which each observation was weighted by the corresponding value of the Bisquare function of the residual from the last iteration. The procedure converged in every case, and reduced the weight of 3.6% of the observations by more than 2/3 (with no significant differences between groups). Ordinary least-squares regression analysis provided comparable results. However, the robust method ensured that the estimates for the patients was not driven by sporadic outliers.

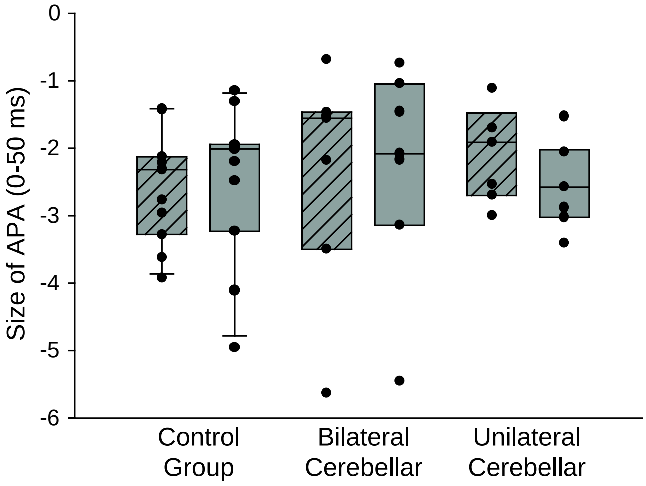

Figure 2.7: *Size of the APA, calculated as the slope of the regression line in Figure 6. Results are shown separately for trials in which the postural hand was the non-dominant (hatched) or dominant (non-hatched) hand. For the unilateral cerebellar patients the data are split into the ipsilesional (hatched) and contralesional (non-hatched) hand. Dots indicate the values for the individuals.*

I compared the values of each hand with the performance of controls averaged across hands. Neither the APA in the ipsilesional hand, $t(16) = 1.24$, $p = .23$, nor in the contralesional hand, $t(16) < 1$, differed significantly from that observed in the control participants.

Each patient showed some scaling of the APA with the speed of the unloading. After accounting for variation in the size of the initial impulse, the overall variability of the APA can be assessed by the spread of the residuals around the regression line. The SD of the residuals was 0.29 N in healthy controls and was significantly increased in the bilateral degeneration patients (0.41 N), $t(16) = 2.68$, $p = .016$. However, the unilateral patients did not show a significant difference in the variability between hands (0.37 N vs. 0.32 N), $t(6) < 1$, nor a significant difference relative to the control group, $t(16) = 1.36$, $p = 0.19$. In sum, both the overall gain of the APA and the scaling relationship between unloading action and the APA appear to be preserved in patients with cerebellar lesions.

2.4.5 Onset of the APA

To quantify the time of onset of the APA, I chose the time at which the average inverse force generated by the postural hand fell below the value of 4.8 N for more than consecutive 40 ms. The temporal criterion was included to exclude spurious fluctuations in force.

Clear differences were observed between the controls and patients on this temporal measure (see Figure 2.5 and Figure 2.8). Using the described ANOVA to compare the controls and patients with bilateral cerebellar degeneration, a main effect was found for the

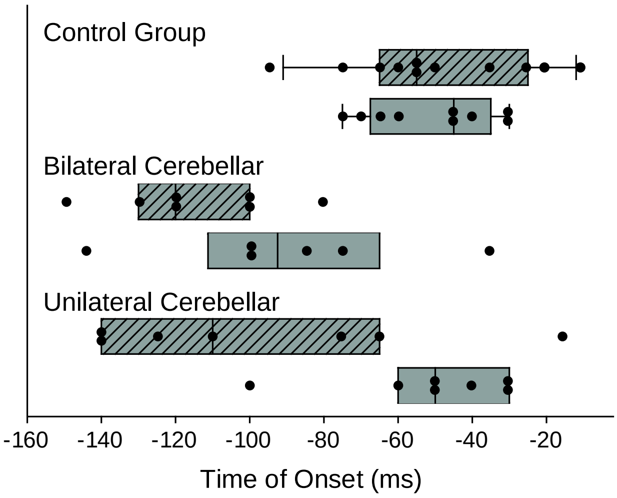

Figure 2.8: *Onset time of the APA, shown separately for trials in which the non-dominant hand (hatched) or dominant hand (non-hatched) was used as the postural hand. For the unilateral cerebellar patients the results are presented for the ipsilesional (hatched) and contralesional (non-hatched) hand as the postural hand. Dots refer to individual values.*

group factor, $F(1, 15) = 19.70$, $p < .001$. APA onset was earlier for the bilateral patients compared to the controls. It was also earlier when the non-dominant hand served as the postural hand, $F(1, 15) = 5.84$, $p = .028$, while the Group x Hand interaction was not significant, $F(1, 15) = 2.11$, $p = .166$.

For the unilateral patients, the within-participant difference between the hands was not significant, $t(6) = 1.85$, $p = .114$. Compared to control participants, however, APA onset was significantly earlier for the ipsilesional hand, $t(16) = 3.31$, $p < .004$, but not for the contralesional hand, $t(11) < 1$. Thus both patient groups showed an earlier onset of the APA than comparable healthy control participants.

For the control participants there was a significant correlation between the size and the onset time of the APA ($r = 0.47$) — the larger the APA, the earlier the onset. This relationship may, in part, reflect the fact that I used a fixed criterion for the onset of the APA[3]. However, this relationship cannot account for the finding that patients showed a premature onset of the APA given that the patients showed a slightly reduced APA.

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[3] Two alternative methods were also used to determine APA onset. The threshold criteria can be made relative to the size of the mean APA, with onset recorded as the first time the inverse force is 20% of that value. This method reduces the correlation between size and onset for healthy controls, but induces a negative correlation in the bilateral patients. The latter occurs because the bilateral patients do not show the same correlation between APA size and onset time. Alternatively, one can determine the onset of the APA in each trial individually. This results in rather variable estimates from trial to trial. Analyses based on the relative criterion or based on the median onset time from the individual trial method led to qualitatively similar results.

Furthermore, the relationship between size and onset disappeared for the patients, $r = 0.10$, providing converging evidence that the effects of APA size and timing are dissociated in patients with cerebellar damage, with only the timing appearing abnormal.

To test for increases in the variability of the onset times I determined the onset based on individual trials (see Footnote 3). The standard deviation of APA onset times was 63 ms in normal controls and 61 ms in bilateral patients. Only the unilateral patients showed a slightly increased variability in the time of onset in their ipsilesional (79 ms) compared to the contralesional (63 ms) hand, $t(6) = 2.62$, $p = .039$.

2.4.6 Adjustments after trick trials

Modulations in the size of the APA, independent of the size of the unloading impulse, can be observed in the residuals from the regression depicted in Figure 2.6. Positive residuals correspond to trials in which the APA was smaller than for a typical trial of that unloading speed; negative residuals correspond to a reduction in the internal force, i.e. a larger APA. Figure 2.9 shows the average residuals for trick trials (lag = 0), and for those trials that preceded or followed the trick trials. The residuals on trick trials were consistently positive. This could be due to inaccuracies in the calculation of the internal force or possible feedback mechanisms that prevent larger reductions in internal force on trick trials[4].

A carry-over effect from the trick trials was present for the control participants. The APA was smaller on the trial immediately following a trick trial (Lag = 1) and then slowly returned to baseline over the course of the next few trials. In contrast, the patients with bilateral cerebellar degeneration, as well as the unilateral patients when the impaired hand was the postural hand, failed to show this short-term adaptation effect. In terms of the unloading action, the initial unloading impulse was unaffected by trick trials for all of the groups. Note that the estimates of the size of the APA at all non-zero lags were based on the same mixture proportion of trick and non-trick trials.

To statistically evaluate these effects, I compared the average residual value for Lag-1 trials with the other lags. This difference was highly significant for the control participants, $F(1, 10) = 22.99$, $p < .001$, but not for the bilateral degeneration group, $F(1, 6) < 1$. To compare control group and bilateral patients directly, I performed a repeated measures ANOVA with group as a between subject and lag (Lag 1, other) as a within subject factor. Both the lag effect, $F(1, 16) = 15.48$, $p = .001$, and the Group x Lag interaction were significant, $F(1, 16) = 8.95$, $p = .009$.

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[4] There was a slight difference between normal and trick trials before the start the unloading: if the hand was lowered in anticipation of unloading, the downward acceleration of the object led to a small reduction of force (see Figure 2.2a). In trick trials the force was kept artificially constant, and this led to a larger downward displacement of the hand (Figure 2.2c). These effects might result in an increase in the internal force on trick trials and would be especially pronounced in the cerebellar patients given that the downward acceleration occurred earlier in this group (see Figure 2.5c).

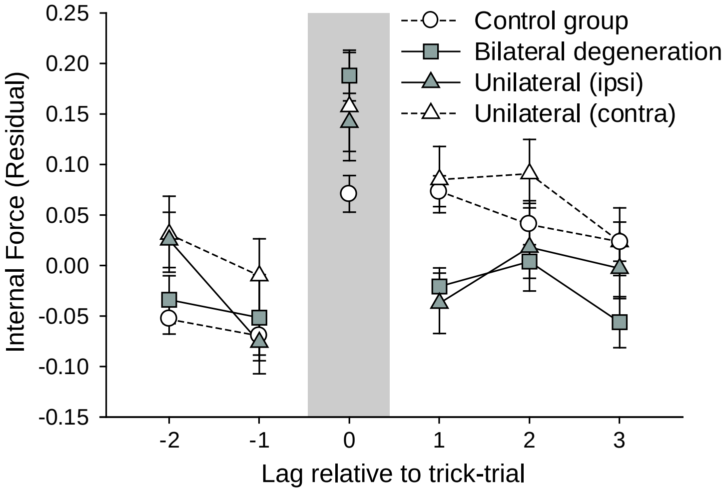

Figure 2.9: *Size of the APA on trick trials (Lag 0) and on trials preceding the trial trial (Lags -2 to -1) and immediately following the trick trials (Lag 1 to 3). Positive numbers indicate a smaller APA, calculated as a smaller decrease in force than expected for an action of a given impulse size (see text).*

Most convincingly, the short-term adaptation effect was absent in the unilateral patients when the postural hand was ipsilesional. In a repeated measures ANOVA with factors hand (Ipsi vs. Contralateral) and lag, the Hand x Lag interaction was significant, $F(1, 6) = 8.63$, $p = .026$. As can be seen in Figure 2.9, these patients showed an adaptation effect comparable to normals when the postural hand was contralesional.

2.4.7 Performance of the callosotomy patient

As can be seen in Table 2.3, the callosotomy patient unloaded the object at speeds comparable to normal participants, although this patient showed a rather restricted range of unloading speeds. Figure 2.10 indicates the main result: the clear presence of the APA. The slope of the regression line, an indicator of the size of the APA was -3.1 for her left and -2.3 for her non-dominant right hand. This is clearly in the range of the healthy controls (Figure 2.8). The onset determined on combined traces was -85 ms. Estimated from individual trials the median onset was -60 ms, and the SD of 64 ms fell well within the range of the other groups.

It may be possible that the preserved APA found in the callosotomy patient was based on visual information about the onset of the movement that reached the hemisphere contralateral to the postural hand. On a substantial part of the trials, however, the active hand was obscured by the object even before the starting signal was given, so that no visual information was present until the object started moving, a time at which the APA was already measurable. In the second half of the experiment, a starting position of the hand

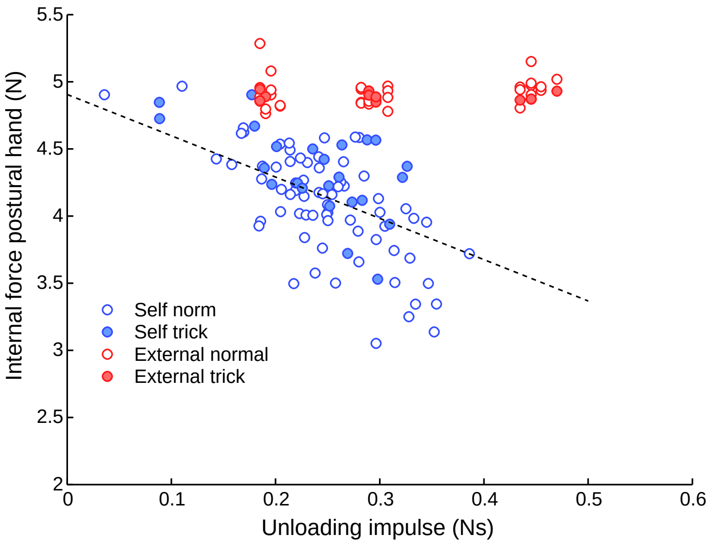

Figure 2.10: *The APA during the bimanual unloading task (data for the right hand in the postural are shown) is clearly present in the callosotomy patient. The regression line (with a constant intercept of 4.9 N) for the self-unloading trials was calculated by pooling trick trials (solid blue) and normal trials (empty blue). External-unloading trials are shown in red.*

that did not allow vision of the active hand was strictly enforced. No difference was found in the mean APA between the blocks of the first and second half, $t(7) < 1$.

2.5 Discussion

The current findings replicate an earlier report of a preserved APA in the bimanual unloading task after callosotomy (Viallet et al., 1992), and show additionally that the timing and scaling relationship of the APA appears to be within the range of normal performance. This suggests either that one hemisphere alone can coordinate the actions of the unloading and postural hands or that the commands to the two hands are coordinated through a subcortical site. To investigate the possible role of the cerebellum as this subcortical site, a group of patients with bilateral cerebellar degeneration, and patients with unilateral cerebellar lesions were tested. While the overall response was preserved in both patient groups, the results indicate a role of the cerebellum in the timing and short-term modulation of the APA.

2.5.1 Temporal abnormalities

While the APA in the bimanual unloading task was generally preserved in cerebellar patients, the timing of the onset of the response was abnormal. For healthy controls, the lowering of the force in expectation of the unloading occurred 30-60 ms before the impact of the unloading hand on the object. This value is slightly earlier than the onset of the EMG reduction in the biceps of the postural arm in a similar task (see Hugon et al., 1982). For the cerebellar patients, the onset of the APA was earlier, in some cases more than 100 ms prior to the beginning of the unloading action.

Evidence for a range of tasks suggests that the cerebellum is involved the timing of movement components across joints. For example, when throwing a ball with an overarm pitch, the opening of the finger is timed so that the ball is released when the hand is in the vertical position (Hore, Watts, Martin, & Miller, 1995). In patients with cerebellar lesions, the temporal variability of the release point with respect to the position of the hand is significantly increased (Timmann, Watts, & Hore, 1999), causing the throws to be less accurate.

Diener et al. (1989) studied anticipatory postural adjustments in stance prior to when the arms are raised to be parallel to the ground. To counteract the resultant interaction torques, the tibialis anterior (ankle flexor) is activated prior to the deltoid muscle (prime mover for arm raises) by more than 50 ms. As in the present study, patients with bilateral cerebellar atrophy showed an overall preserved anticipatory response, but the timing of the response was abnormal: the burst of the tibialis anterior often preceded the action by more than 100 ms and sometimes even subsided by the time the perturbing effects of the arm movement were experienced. This poor timing led to postural instability.

A third example comes from a bimanual behavior: opening a drawer and reaching in with the other hand to retrieve an object. While healthy subjects time the opening and retrieving action so that they are optimally coordinated at the goal, (Perrig, Kazennikov, & Wiesendanger, 1999), cerebellar patients are more variable, with a large delay frequently seen between the pulling and grasping actions (Serrien & Wiesendanger, 2000).

Disruption of timing after cerebellar lesions is also evident in eyeblink conditioning in the rabbit (Perrett, Ruiz, & Mauk, 1993; but see Attwell, Ivarsson, Millar, & Yeo, 2002), for timed rhythmic movements (Ivry, 1997; Ivry & Keele, 1989; Ivry, Keele, & Diener, 1988; Spencer, Zelaznik, Diedrichsen, & Ivry, in press), perceptual judgements of temporal intervals (Ivry, 1996; Ivry & Hazeltine, 1995; Mangels, Ivry, & Shimizu, 1998), and speech perception (Ackermann, Graeber, Hentrich, & Daum, 1997). The generality of temporal abnormalities has led to the hypothesis that the cerebellum is involved in the relative timing of discrete neural events in both motor and non-motor tasks (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002).

How would the cerebellum accomplish the temporal coordination of movement components across joints? One interesting feature of the current results is that the APA occurs consistently early in cerebellar patients. This result is similar to that seen in other timed movements (Diener et al., 1989; Perrett et al., 1993; Timmann et al., 1999).

One hypothesis is that the premature onset could reflect a safety strategy: If lesions to the cerebellum lead to inaccuracies in timing (Ivry et al., 2002), the early onset of the APA might increase the likelihood that the response is initiated prior to the unloading. However, in the current study the variability of onset times was only increased for the unilateral patients.

Alternatively, the early onset of these behaviors might reflect the general mechanism by which the cerebellum ensures accurate timing across different joints and modalities. As suggested by Thach and colleagues (Thach et al., 1992) activity in the deep cerebellar nuclei may reflect possible components of an action. The release of inhibitory input from Purkinjie cells might trigger these components in the right moment relative to each other. Following damage to this inhibitory system, the correct action components would be released, but the adaptive timing, normally ensured by the cerebellar cortex, would be perturbed. This would lead to an early initiation in respect to a stimulus, as is the case of eyeblink-conditioning (Perrett et al., 1993) or in relation to a voluntary action as found here (see also Diener et al., 1989). According to this hypothesis, the cerebellar cortex coordinates action not by actively introducing new movement components, but rather by sculpting the preexistent response (Thach et al., 1992).

2.5.2 Modulation based on recent experiences

In healthy control participants the size of the APA was reduced after the experience of a downward deflection of the hand on trick trials. This adjustment was absent in the bilateral cerebellar patients and in the unilateral patients when the postural hand was ipsilesional.

This finding provides support for the hypothesis that the cerebellum adaptively adjusts motor behaviors according to changes in the environment. Deficits in motor adaptation can be found for example when patients are asked to throw balls at a target while wearing prism glasses. Unlike healthy participants, cerebellar subjects fail to adapt to the lateral displacement introduced by the prism glasses and do not show an aftereffect, when the prisms are removed (Martin, Keating, Goodkin, Bastian, & Thach, 1996).

Another example of a failure to adapt can be observed when cerebellar patients are asked to catch a falling ball with an outstretched hand. Healthy participants show anticipatory activation of the flexor muscles of the forearm (Lacquaniti & Maioli, 1989a, 1989b). Cerebellar patients showed a residual anticipatory response, but failed to use predictable changes in weight of the object to adapt their responses (Lang & Bastian, 1999). Added sensory information about drop-height and weight of the ball did not alleviate these deficits (Lang & Bastian, 2001), making it unlikely that sensory deficits can account for this failure.

The inability to adjust motor behaviors seems intimately related to the failure of cerebellar patients to learn new coordination tasks (see Chapter 4). The architecture of the cerebellum seems to be especially suitable for rapid modification of motor behaviors, in our case changes that occur with one trial of unexpected sensory feedback.

2.5.3 Preserved APA after cerebellar lesions

It is important to keep in mind that, despite their problems in timing the APA, the cerebellar patients (with the exception of the non-dominant hand of one bilateral degeneration patient) did exhibit an anticipatory response. This was most clearly shown by the downward deflection of the postural hand on trick trials. Moreover, as a group, the size of the APA was similar to that observed in the control participants. Neither the ataxia rating nor the extent of the lesion correlated with the size of the APA. Even in the three patients with damage to the dentate nucleus, the APA did not appear to be reduced in size. The cerebellar group also showed normal speed-dependent scaling of the APA. The decrease in the torque generated at the elbow joint of the postural arm reflected the speed at which the unloading hand approached and lifted the object.

These findings may suggest that the internal representation that generates the APA is stored outside of the cerebellum. Humans are not born with the ability to produce an anticipatory postural adjustment in the context of the bimanual unloading task; the anticipatory behavior is acquired rather late in life, between the age of 5 and 7 (Schmitz, Martin, & Assaiante, 2002). While it is likely that the cerebellum was involved in the acquisition of this response (see Chapter 4), the actual generation of the APA may be independent of cerebellar structures.

The debate whether new motor behaviors are stored in the cerebellum or if it is only involved in acquisition and modification of these patterns is central in many areas of cerebellar research. For example, it remains unclear whether lesions to the cerebellar cortex abolish previously learned conditioned eye-blink responses or only impair the acquisition of new ones (Attwell et al., 2002; Perrett et al., 1993; Woodruff-Pak, Lavond, & Thompson, 1985). For human subjects it has been found that cerebellar damage impairs the acquisition of a new conditioned eyeblink reflex. However, a conditioned eyeblink response that is acquired very early in life, the closure of the eyes when viewing a rapidly approaching stimulus, was unimpaired in the same subjects (Bracha, Zhao, Wunderlich, Morrissy, & Bloedel, 1997). However, in this and the current study, the extent of the lesion to the deep cerebellar nuclei, especially to the fastigial and interpositus nucleus, was hard to assess. The possibility remains that the APA would be severely reduced after complete damage to all cerebellar structures.

Other structures that might play a role in the generation and storage of the APA include motor cortex or SMA contralateral to the postural hand, consistent with the observation of pronounced deficit in the generation of APAs in hemiplegic patients (Bennis et al., 1996; Viallet et al., 1992). To account for the relatively preserved coordination between the hands in callosotomy patients, information about the timing and scaling of the upcoming action has to be transmitted subcortically. Subcortical projection targets of the cerebellum, for example the red nucleus or the reticular formation, have been implicated in postural control (Prentice & Drew, 2001). Such a broadened subcortical network for anticipatory postural control would explain the seeming robustness of this behavior to neurological damage.

Chapter 3

Is an efference copy necessary for learning?

3.1 Abstract

In the unloading task, a weight is held in the palm of one hand. When an external agent removes the weight, an upward perturbation of the loaded hand is observed. However, when a person removes the weight by lifting it with their own hand, the perturbation is attenuated due to an anticipatory adjustment of the flexor muscles in the load-bearing arm. An experiment was conducted to examine conditions under which this anticipatory response could be learned. Using a virtual reality system with force-feedback robotic arms, normal subjects performed the unloading task under one of four learning conditions: (a) the participant initiated the unloading by pressing a button, (b) the unloading was cued by a brief visual stimulus, (c) the unloading was performed by a virtual "hand" that moved smoothly towards the object, (d) the unloading followed three rhythmic force-pulses applied to the finger of the participant. After extended practice (192 trials) a significant reduction of the upward perturbation only was found in the button pressing condition. Control conditions indicated that the acquired response was due to an anticipatory feedforward response rather than due to a change in tonic state such as an increase in arm stiffness. These results indicate that a voluntary action is necessary to acquire an anticipatory adjustment in the unloading task.

3.2 Introduction

Anticipation is a fundamental characteristic of the human motor system. Changes in the environment or in posture constantly alter the forces that affect our limbs. We are able to prevent the resulting limb instabilities by adjusting muscular activation, even before proprioceptive or kinesthetic information is available. For example, to prevent slippage, grip-forces are adjusted when changes in the weight of an object can be anticipated (Blakemore, Goodbody, & Wolpert, 1998; Johansson & Westling, 1984, 1988). In the "unloading task", where one hand unloads a weight held by the other hand, the loaded muscles show an anticipatory decrease in activity (Lum, Reinkensmeyer, Lehman, Li, & Stark, 1992; Massion, 1984). Generating such anticipatory adjustments (APA) requires a controller that predicts the expected perturbation based on an efference copy of the voluntary action (Miall & Wolpert, 1996; Wolpert & Kawato, 1998). This prediction can then be used to generate the appropriate adjustment to counteract the perturbation.

One of the fundamental issues of anticipatory motor behavior is whether these adjustments only occur when the perturbation is self-produced or whether these adjustments can be performed when the perturbation is made predictable by sensory information. This issue is theoretically important as it pertains to the question of how to characterize the controllers governing anticipatory motor behaviors. According to an "encapsulated process" view, the APAs are an integral part of the voluntary action that leads to the perturbation (e.g. Aruin & Latash, 1995). Thus, the anticipatory response can only occur in conjunction with the eliciting action. In contrast, a "parallel process" view conceptualizes the controller of the anticipatory adjustment as being accessible to other inputs. Under this view, the controller can also learn to react to perturbations that are predictable on the basis of incoming sensory information.

Anticipatory adjustments of grip and load forces are only present when the perturbation is self-elicited (e.g. Aruin & Latash, 1995; Struppler, Gerilovsky, & Jakob, 1993). Anticipatory changes in muscular activity are not observed when the perturbation is signaled by an auditory tone (Dufossae, Hugon, & Massion, 1985; Witney, Goodbody, & Wolpert, 1999) or when the force changes are generated externally in a predictable, sinusoidal manner (Blakemore et al., 1998). In contrast, when catching a falling object, a sizable anticipatory response to the expected impact is observed even if the release of the object is not self-produced (Lacquaniti & Maioli, 1989a, 1989b; Shiratori & Latash, 2001). These adjustments are triggered solely by the visual information provided from the falling object.

The failure to find APAs in grip and load forces prior to predictable external perturbation (Dufossae et al., 1985; Struppler et al., 1993; Witney et al., 1999) may be due to two factors. First, the sensory signals may not have provided sufficient information concerning the timing of the forthcoming perturbation. In the aforementioned studies, discrete auditory signals indicated the time of the disturbance. A similar discrete signal was insufficient to elicit an APA prior to catching, whereas observing the whole trajectory of the ball from release to impact was sufficient (Lacquaniti & Maioli, 1989a). Providing predictive information in a continuous manner might elicit APAs in the unloading task. Second, some amount of exposure to the predictable external perturbation may be crucial for acquiring an appropriate APA. Paulignan et al (1989) studied anticipatory changes when the unloading of a weight was self-initiated by a button press performed by the other hand. After several hundred trials of practice, participants were able to acquire an anticipatory response. Thus, substantial training with a predictable external perturbation may also lead to the acquisition of an APA.

To evaluate different methods for signaling a forthcoming force perturbation in the unloading task under extended practice I used a visual-haptic virtual-reality environment (see Figure 3.1a, Methods). There were four training protocols, all involving situations in which the load was removed by an external force. In the vision-discrete condition, the color of the object changed 300 ms before the start of unloading. In the vision-continuous condition participants saw a virtual robotic arm approaching (over a 600 ms window; speed increasing monotonically) and upon contact unloading the object. This condition was designed to mimic the continuous visual information available when catching an object. In the volitional-action condition, unloading was triggered when the participant pressed a button with their other hand. Finally, in the haptic condition, participants also pressed a button, but here this response initiated a series of three rhythmic force pulses delivered to the finger at a rate of 600 ms. Unloading occurred simultaneously with termination of the last pulse. This condition was designed to provide similar proprioceptive and haptic feedback as the button-action condition, but without a volitional action that triggers the unloading directly.

I also included two baseline tasks. In natural self-unloading, the participants used their other hand to lift the object. In the external-unloading condition, no cues were provided to indicate the onset of the unloading.

Perturbations following unloading can be attenuated in one of two ways. The participant may either generate an anticipatory response consisting of the relaxation of the load-bearing muscles or the stiffness of the load-bearing arm can be increased (Biryukova et al., 1999). To distinguish between these two responses, I included "trick" trials. For these, the same cues were provided as on regular trials and the visual image of the object was displaced when force was applied to it. However, the weight on the loaded hand did not change. If participants relaxed the load-bearing muscles in an anticipatory fashion, their arm would be deflected downward on trick trials given the absence of the expected weight displacement. On the other hand, if the arm is stiffened, no perturbation should be observed on regular or trick trials.

3.3 Method

3.3.1 Participants

Thirty-two students (17 male, 15 female, mean age = 22.7 years, 2 left-handed) from the University of California, Berkeley were recruited and financially compensated for their time. All participants were naive to the purpose of this study. Approval for the project was granted by the local Committee for the Protection of Human Subjects.

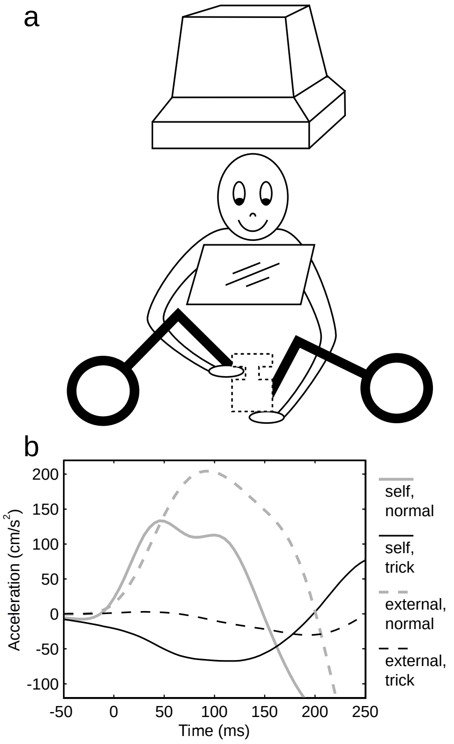

Figure 3.1: *(a) Experimental apparatus. A virtual object was presented on a monitor, which participants viewed via a mirror. The index fingers of each hand were connected to a programmable robot arm (SensAble Technologies), which simulated the forces generated in the interaction with the virtual object (dashed outline). (b) Acceleration functions for self-unloading and external-unloading trials, averaged over pre- and post-training phase and the four different conditions. Traces are aligned to the onset of unloading (0ms). Standard trials (gray) lead to an upward perturbation, whereas trick trials (black) lead to a downward perturbation indicating a feedforward postural adjustment.*

3.3.2 Apparatus and stimuli

Participants viewed a virtual 3-D environment displayed on a 24" computer monitor reflected by a mirror through stereoscopic shutter glasses (80-120 Hz). Within a 20 x 20 x 22 cm workspace, participants saw a virtual object. This object was a 5-cm cube with a T-shaped handle connected to the top surface (2 cm wide at the neck, 4 cm wide at the handle). In addition, the workspace included two 0.8 cm spheres, corresponding to the positions of the two index fingers and, in the volitional action and the haptic condition, a 4 x 1.5 cm button, appearing on the floor of the workspace, 6 cm from the object.

Each index finger was linked to a robotic arm (PHANToM 1.5 System (r), SensAble Technologies). These robots were used to simulate interactive forces. For the cube, these forces were created by assuming an object weight of 330 g. For the button, the forces were created to simulate a spring constant of 0.5 N/m over a 0.7 cm travel distance for full depression. Measurements of each finger's position and force were sampled at 200 Hz.

3.3.3 Procedure

To initiate each trial, the participant placed one hand under the base of the object, lifted it about 3 cm off the floor, and maintained this position for 1.5 s. In the self-unloading condition, the handle turned red and the participant was instructed to lift the object with the other hand. In all other conditions, the object was displaced upward by the computer. This displacement occurred in a stereotypical manner[1], based on pilot work to define the shape and speed of natural unloading.

Participants were assigned to one of four training conditions. Before and after training, participants completed six blocks: self unloading, external unloading, and a block in their specific training condition. Each of these was performed once with the left and once with the right hand supporting the object. Each block consisted of 24 trials, 16 standard trials and 8 randomly interspersed trick trials. The block sequence was counterbalanced across participants. Training was limited to either the left or the right hand and consisted of eight blocks of 24 trials. No trick trials were included during training.

3.3.4 Data analysis

Position and force traces of each trial were aligned to the start of unloading, defined by the moment when force was applied to the object either by the other hand or the computer. Traces were averaged for each block[2], with separate averages created for normal and trick trials during the pre- and post-training phases. The largest perturbation of the postural hand relative to a 200 ms baseline window prior to unloading was determined. Peak acceleration before maximal perturbation was also calculated (Lum et al., 1992). The time between the start of the unloading action and the moment at which the lifting force reached 85% of the object's weight was used as a measure of unloading rate.

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[1] The unloading by the computer was achieved by applying a virtual force to the object that increased smoothly and reduced the force on the loaded hand by 85% within the first 176 ms. The force increased in a negatively accelerated fashion according to the formula:

$$F(t) = \left\{ 1 - e^{-5.4 \cdot t} \cos(7.6 \cdot t) \right\} 330\, g \cdot 9.81 \frac{m}{s^2}$$

[2] I also estimated the size and time of maximal acceleration based on individual trials. While this method yielded higher estimates of acceleration, the overall pattern of results was similar to that presented in the main text.

3.4 Results

The self and external unloading trials provide a baseline measure of performance. To approximate the mean rate of self-unloading trials to the rate of the external unloading trials (176 ms), I selected a subset of the self-unloading trials in which the speed was faster than 250 ms (69% of all trials). For non-trick trials, peak acceleration was greater in the external unloading condition (207 cm/s^2) than in the self-unloading condition (137 cm/s^2), $F(1, 28) = 48.62$, $p < .001$ (Figure 3.1b). On trick trials, the downward acceleration was higher for self unloading (-90 cm/s^2) than external unloading (-49cm/s^2), $F(1, 28) = 25.40$, $p < .001$, and also occurred substantially earlier (150 ms vs. 201 ms post-unloading), $F(1, 28) = 57.44$, $p < .001$. None of these measures differed between groups, (all $F < 1$) nor did they vary significantly between pre- and post test (all $F < 2.2$). These results indicate that that I was successful in replicating the basic features of the unloading task in our virtual environment.

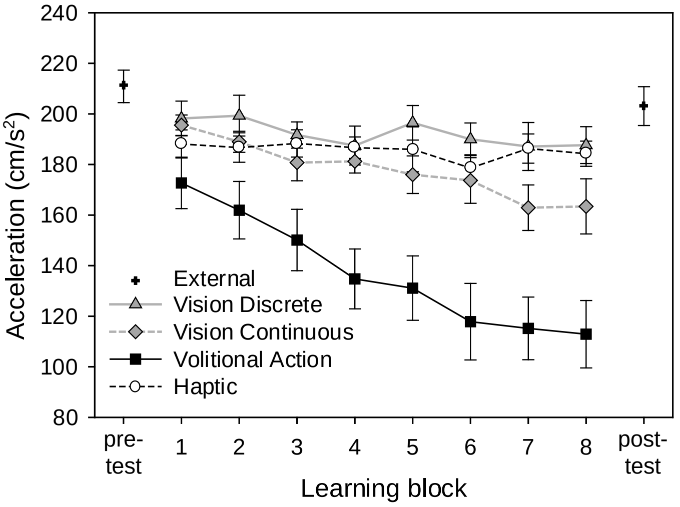

Figure 3.2: *Average peak acceleration for the four conditions in the learning phase. The values of external unloading in pre- and post-test for the trained hand are shown as baseline. Error bars indicate between-subject standard error.*

I next analyzed changes in performance over the training blocks (Figure 3.2). A two-factor ANOVA verified a significant mean difference between conditions, $F(3, 28) = 10.0$, an effect of block, $F(7, 196) = 25.50$, and a Condition x Block interaction, $F(21, 196) = 6.17$, (all $p < .001$). A linear regression for each condition revealed statistically significant learning for the volitional-action condition, $F(1, 62) = 23.64$, $p < .001$, and less, but still significant, learning for the vision-continuous condition, $F(1, 62) = 17.09$, $p < .001$. No reduction in peak acceleration was observed in the vision-discrete, $F(1, 62) = 2.05$, $p = .156$, and in the haptic condition, $F(1, 62) = 0.64$, $p = .42$.

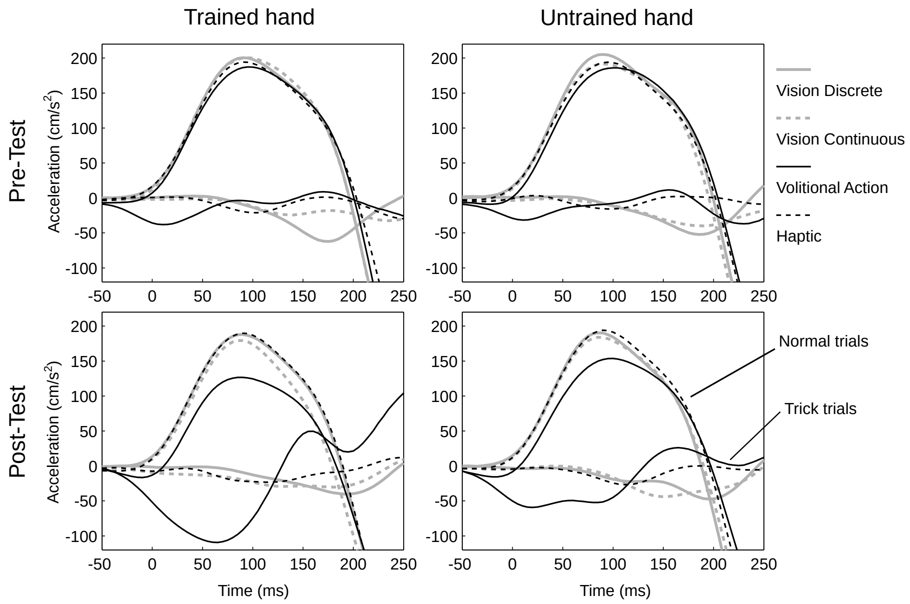

Figure 3.3: *Acceleration functions for the four learning conditions in pre- and post-training and for the trained or untrained hand. Only the volitional-action (black solid) condition showed substantial reduction of upward acceleration in standard trials and a trick response indicating a feed-forward anticipatory adjustment.*

Learning was assessed by comparing pre- and post-test performance in a Condition x Phase x Hand (trained vs. untrained) ANOVA. On non-trick trials, the difference in maximum acceleration between pre- and post test interacted with condition, $F(3, 28) = 9.57$, $p < .001$. This interaction reflected the fact that a significant reduction in maximum acceleration was only observed in the volitional-action condition (see Figure 3.3). Moreover, this reduction was more pronounced in the trained hand than in the untrained hand, $F(3, 28) = 4.75$, $p = .008$, indicating that much of the learning was effector-specific.

The trick trials provide further evidence that a true APA was only acquired in the volitional-action condition. Following training, the size of the downward acceleration was greater for this condition than in the external unloading condition, $t(7) = 3.51$, $p < .001$. No other condition showed a change in the trick response (all $t(7) < 0.5$). Moreover, maximal downward acceleration occurred 100 ms earlier in the volitional-action condition than in the other three conditions, $F(3, 28) = 3.34$, $p = .033$.

3.5 Discussion

In this study, the prerequisites for acquiring an anticipatory adjustment in the unloading task were investigated. A feedforward APA was only learned when the unloading was directly triggered by a volitional button press. We also found a significant reduction in maximum acceleration during training in the continuous-vision condition. However, the lack of a change from pre- to post-test for standard and trick trials in this condition suggests that this learning was not of an APA but rather of a correctly timed increased stiffness of the postural arm.

These results indicate that the development of an APA is dependent on its association with a volitional action, even when the relationship between the action and it's consequence is fairly abstract (Aruin & Latash, 1995; but see Dufossae et al., 1985).

The failure to find an APA in the absence of a volitional action is consistent with a number of other studies (Aruin & Latash, 1995; Blakemore et al., 1998; Dufossae et al., 1985; Struppler et al., 1993; Witney et al., 1999). The current results extend this by showing that an APA is still not learned even with highly predictive sensory information and extended practice. In contrast to the results from unloading and force grip tasks, it does appear that an APA can be elicited solely on the basis of visual information during ball catching (Lacquaniti & Maioli, 1989a, 1989b; Shiratori & Latash, 2001). Ball catching may be qualitatively different in nature to unloading (Dufossae et al., 1985) or grasping (Blakemore et al., 1998; Witney et al., 1999). Moreover, as pointed out by Aruin and Latash (1995), small movements of the catching hand towards the ball could help trigger the APA in ball catching, blurring the distinction between a voluntary action and the anticipatory adjustment.

Further evidence that anticipatory adjustments associated with ball catching and unloading are qualitatively different comes from probes of intermanual transfer. If the APA is an integral part of the triggering action, one would expect learning to be specific to the executing hand. In contrast, nearly complete inter-manual transfer might be demonstrated if the behavior is governed by a more abstract representation (Gordon, Forssberg, & Iwasaki, 1994; Hemminger, Donchin, Ariff, Young, & Shadmehr, 2001; Shadmehr & Mussa-Ivaldi, 1994). For ball catching, Morton et al. (Morton, Lang, & Bastian, 2001) reported an inter-manual a transfer rate of 68 %. In the current study, the intermanual transfer score in the volitional-action condition was only 36%[3](see also Ioffe, Massion, Gantchev, Dufosse, & Kulikov, 1996). The substantial transfer during ball catching suggests that the APA associated with this task relies, at least to a higher degree than in the unloading task, on external task parameters (ball height, impact time) rather than on internal sensorimotor parameters (dynamics of hand-ball interactions).

The current results are consistent with the view that during unloading the process

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[3] For the non-trick trials, transfer was calculated as

$$\frac{Acc_{Untrained,post} - Acc_{Trained,L1}}{Acc_{Trained,post} - Acc_{Trained,L1}} \cdot 100$$

Acc is the peak acceleration in the first learning block (L1) and the post-test (post). For trick trials, this measure could not be calculated, as they were not included in the learning phase.

generating the anticipatory adjustment is linked to the action required for the arbitrary button press. It remains unclear why the same process could not be similarly linked to predictive sensory events. Impairments in the acquisition of such adjustments would prove useful in identifying the neural structures involved in the development of internal models for sensorimotor control.

Chapter 4

Neural structures involved in the acquisition of a new APA

4.1 Abstract

The role of the cerebellum and the corpus callosum in acquiring a co-ordination between posture and movement in a bimanual task was investigated. Participants supported a virtual object in one hand. When they pressed a button with the other hand, the object was lifted, unloading the postural hand of the object's weight. Prior to training, the postural hand was displaced in an upward direction. After 30 min of training, age-matched control participants showed a reduced upward perturbation. This was due to an anticipatory deactivation of forearm flexor muscles, as evidenced by a downward perturbation on "trick"-trials in which the button press did not lead to a load release. Participants with bilateral degeneration of the cerebellum or unilateral damage to the cerebellum ipsilateral to the postural hand did not acquire the anticipatory postural adjustment (APA). In contrast, a callosotomy patient learned to produce an APA in association with the button press. This study provides novel evidence that the cerebellum, but not the corpus callosum, is necessary to learn a new anticipatory postural adjustment (APA) during bimanual actions.

4.2 Introduction

When producing movements, we take into account the destabilizing effect of the action of one limb on the state of rest of the body. For example, when raising an arm to the horizontal position, the ankle flexors show activity to compensate for the interaction torques that would destabilize the body (Belenkiy, Gurfinkel, & Paltsev, 1967; Bouisset & Zattara, 1987). Feedback mechanisms are too slow to counteract such perturbations efficiently. Rather, adjustments are implemented in a feedforward manner, based on predictions of the upcoming perturbation. Such anticipatory postural adjustments (APAs) can also be observed during bimanual actions. When holding a jar with the left hand and opening the lid with the right, the grip force of the left hand increases at the right time and with the appropriate intensity to prevent slippage (Witney, Goodbody, & Wolpert, 2000).

The ability to predict and counteract a self-induced perturbation is learned through interactions with the environment during childhood (Massion, 1998). Schmitz et al. (2002) performed a cross-sectional study on children of ages 4-8 on APAs during bimanual unloading. In this task, participants hold an object with one hand and then lift it with the other hand. The forces generated by the postural arm must be reduced in time to prevent an upward perturbation of the hand (Dufossae, Hugon, & Massion, 1985; Hugon, Massion, & Wiesendanger, 1982; Massion, Ioffe, Schmitz, Viallet, & Gantcheva, 1999). While small anticipatory changes in the EMG pattern were visible in the postural arm of 4-year olds, the behavior did not reach the full adult-like pattern until 8 years of age. Early in learning, stability was maintained by co-contraction of the agonist and antagonist muscles. For the older children and adults, the dominant pattern was the more efficient anticipatory reduction of activity in the flexor muscles. The acquisition of other anticipatory modulations of motor behavior seems to follow a similar developmental course (Eliasson et al., 1995; Forssberg et al., 1992).

The goal of the current study is to elucidate the neural structures that are involved in the acquisition of an APA associated with bimanual coordination. The memory trace of the APA acquired in childhood is rather robust against neurological damage and may be supported by a network of neural structures, including the motor cortex, SMA, the cerebellum, and basal ganglia. A number of studies have shown that the APA is disrupted after a stroke to the hemisphere contralateral to the postural hand (Bennis, Roby-Brami, Dufosse, & Bussel, 1996; Viallet, Massion, Massarino, & Khalil, 1992). At the same time split brain patients show largely preserved APAs during the bimanual unloading task (Viallet et al., 1992; Chapter2), indicating the involvement of a subcortical anticipatory network. Damage to the cerebellum leads to deficits in the timing and adjustment of the APA, but does not abolish it (Chapter 2), arguing that this structure plays a modulatory role. Furthermore, Parkinson patients show a reduction in the size of the APA although the response pattern is still preserved (Viallet, Massion, Massarino, & Khalil, 1987).

Few studies have investigated the neural systems directly involved in process of learning a new APA. To study the acquisition of APAs in adult participants, an indirect version of the unloading task has been used. In this task the postural hand again supports an object but the other hand now triggers the unloading by closing a switch rather than lifting the object directly. Healthy participants typically learn anticipatory stabilization of the postural hand over the course of 60-100 trials (Chapter 3, Paulignan, Dufosse, Hugon, & Massion, 1989).

In one study (Massion et al., 1999) Parkinson patients and hemiparetic patients with cortical or internal capsule damage were tested on the indirect unloading task. While the Parkinson patients were impaired at the acquisition of the APA, they did show some residual learning. In contrast, when hemiparetic patients were tested with the contralesional hand as the postural hand, they failed nearly completely to acquire the new anticipatory behavior.

Many questions, however, remain unanswered. Previous work on the acquisition of new bimanual motor skills in split brain patients has suggested that intercortical communication through the corpus callosum may be necessary to establish a new association between the hands (Franz, Waldie, & Smith, 2000; Preilowski, 1972). Alternatively, learning may occur with the help of the subcortical areas involved in the preserved bimanual coordination in callosotomy patients.

The second question concerns the proposed subcortical anticipatory network itself. Massion and colleagues (Massion et al., 1999) suggest a central role of the cerebellum in the learning process. This is a reasonable hypothesis given the involvement of the cerebellum in the acquisition of new motor behaviors and the coordination of movements across joints (for a review see Thach, 1996). However, the role of the cerebellum in the acquisition of a new bimanual coordination has not been tested.

I investigated the acquisition of the APA in the indirect unloading task, testing control participants and patients with either bilateral cerebellar degeneration, or unilateral cerebellar lesions due to tumor or stroke. While most control participants and the bilateral degeneration patients were trained with the dominant hand playing the role of the postural hand[1], the unilateral group was tested with the ipsilesional hand as the postural hand. (In an extension of this work the involvement of the cerebellum in the acquisition of postural adjustments for the contralateral hand will be assessed.) Additionally one callosotomy patient was trained and tested with her dominant as postural hand.

4.3 Method

4.3.1 Participants

Six bilateral cerebellar patients, seven unilateral cerebellar patients and eleven age-matched control participants were tested. All of the participants were included in the study reported in Chapter 2 (see Table 2.1) and the two experiments were performed during the same testing session. One of the degeneration patients (JF) was not able to perform the task due to severe distal ataxia that made him unable to push the button in a reliable fashion. The average severity of the postural & gait disturbances according to the International Cooperative Ataxia Rating Scale (Trouillas et al., 1997) was 12/34 for the bilateral group and 6/34 for the unilateral patients. The average ataxia for upper and lower limb on the

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[1] A pilot study with undergraduate students first hinted at a slight advantage for learning in this configuration. Further testing, however, revealed that this difference was not reliable $t(8) < 1$.

trained side was 8/24 for both groups.

One 50-year old callosotomy patient was also tested. The corpus callosum was resected in 1995 as part of her treatment for severe epilepsy. The patient is left-handed and was on anti-seizure medication during testing. In everyday life she does not report difficulties with bimanual coordination. For example, she was able to tie her shoes two months after the operation, at the same time at which unimanual motor skills recovered.

4.3.2 Apparatus and stimuli

We used a virtual 3-D environment to simulate the visual and haptic aspects of the unloading task. Participants were seated in front of a mirror, through which they viewed a 24" computer monitor. The monitor displayed a virtual workspace (40 cm x 35 cm x 26 cm) that appeared to be located directly in front of the participants. The floor of the workspace was at the height of the participant's knees. The workspace contained a table-like object that consisted of a 20 x 10 x 2 cm handle centered on a 4 x 4 x 7 cm foot. A 4 x 3 x 2 cm button was located on the surface of the workspace, displaced 14 cm lateral from the center of the object.

Each index finger was linked to a robotic arm (PHANToM 3.0 System (r), SensAble Technologies) by placing it in a thimble-like device. The positions of the tip of the fingers were continuously displayed on the appropriate place on the monitor by two 0.8 cm sphere. The robotic system simulated the forces arising from interactions between the hand and the virtual objects at an update rate of 1000 Hz. The table-object could only be moved in the vertical direction and had a weight of 0.34 kg. The button could be depressed over a distance of 2 cm and had a spring with a stiffness of 1.76 N/cm. The position and interaction forces for each finger were recorded on every fifth update cycle, i.e. at 200 Hz. The table-object was supported by the postural arm, with the position of the elbow at approximately 90 deg, the palm facing upward and the middle and index fingers supporting the weight of the object. The other hand rested with the palm facing downward on the participant's leg to promote a stable button press. The key was always pressed using only the index finger.

The movements of both the active and postural arm were unconstrained and involved the finger, wrist and elbow joints. The inverse dynamics method used in Chapter 2 was not employed here because the perturbation was generated in a stereotypic manner by the computer; thus, there was no relationship between the dynamics of the button press action and the unloading event.

4.3.3 Procedure

Using either the left or right hand, participants lifted the object into a visually marked region 3-6 cm above the floor of the virtual workspace. The object had to be maintained in this region for 0.5 s before the next phase of the trial. In the button-press condition, a starting signal was given immediately and the participants pressed the button, which caused the object to lift off the hand. In the external unloading condition, the computer lifted the object after an additional variable interval of 200 ms to 1200 ms, chosen to roughly correspond to the reaction time required in the button press condition. In both cases, the unloading occurred in an invariant manner, by simulating a smooth upwards force on the object that accelerated the object and caused a roughly linear decrease in downward force on the postural hand until the object was no longer in contact with the hand (Figure 4.1). The slow unloading mimics the change in force experienced under natural unloading conditions. Corresponding visual feedback about the position of the table-like object, the button, and both hands was provided continuously.

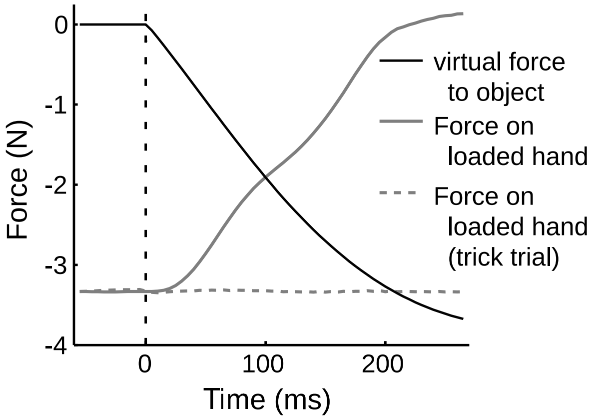

Figure 4.1: *Force functions in the button-unloading experiment (identical for external and button press trials).*

After each trial the participants were provided with feedback about the amount of movement of the postural hand. They were instructed to minimize the perturbation without co-contraction. Occasionally, participants would adopt a strategy in which they dropped the postural hand at the same time they pressed the button. This was monitored by the experimenter and actively discouraged. Trials in which the postural hand achieved a downward acceleration of 0.4 m/s^2 50 ms before the button press were excluded from further analysis.

Without changes in the neural inputs to the postural arm, an upward perturbation will occur when the object is unloaded. Stabilization of the postural hand can be achieved by two means: the anticipatory lowering of the force that holds the object, or by increasing joint stiffness about the elbow through the co-contraction of the agonist and antagonist muscles (Biryukova et al., 1999). On normal unloading trials, either strategy would lead to a reduction of the upward acceleration of the postural hand. To distinguish these two strategies, we included "trick trials" in which the object was lifted with the same force function. The force on the postural hand however was kept constant despite the visual depiction of the object moving upwards and losing contact with the hand. An anticipatory lowering of the force on the postural arm would produce a downward perturbation of the hand on trick trials. In contrast, increases in joint stiffness would not result in kinematic changes on these trials. The response on these trick trials provides a pure measure of the feedforward command to the postural hand (Lum, Reinkensmeyer, Lehman, Li, & Stark, 1992). Once the object reached the ceiling of the workspace (500-600 ms after the start of unloading), the "trick" force applied to the postural hand was removed smoothly. Many participants remained unaware of the inclusion of trick trials.

The experiment consisted of five phases. In the first two blocks each hand was tested on 15 external unloading trials each. These trials provided a baseline measurement of the perturbation of the postural hand when the unloading is not anticipated. In the pre-test phase, the participant elicited the unloading with a button press. Each hand was tested on two blocks consisting of 15 trials, with hands alternating block by block. The learning phase consisted of 8 blocks with 24 button-press trials with only the trained hand holding the object. The post-training test phase was identical with the pre-training test phase. The experiment ended with a baseline measurement on each hand with 15 external unloading trials. In the pre- and post-test blocks, and in the external baseline block, four out of 15 trials were randomly selected to be trick trials. The learning phase did not contain trick-trials, because pilot work indicated that the presence of trick-trials significantly slowed the acquisition of an APA.

The split-brain and all bilateral degeneration patients were trained so that the dominant hand played the postural role. All unilateral patients were trained with the ipsilesional hand serving as the postural hand. The ipsilesional hand was the dominant hand for three of the unilateral patients and the non-domianant hand for the other four. Because of this, three of the controls were also tested with their non-dominant hand used as the postural hand.

4.4 Results

The main dependent variable was the acceleration of the postural hand on trick and normal trials. Acceleration traces were computed by numerical differentiation, filtered with a Gaussian kernel of 1.7 ms FWHM (full width at half maximum) and aligned to the moment of the start of unloading. The average acceleration traces for the trained and untrained hand of the control participants is shown in Figure 4.2. Even in the pretest there was a tendency for the age-matched controls to show a smaller perturbation on button press trials than on the external trials, and a slight downward deflection on trick trials was observed. However, the perturbation is further reduced during the post-test phase for the trained hand. Performance on trick trials makes clear that this reduction was achieved by an anticipatory deactivation of the flexor muscles rather than by co-contraction. For statistical analysis I averaged the acceleration in the time window from -25 ms to 125 ms. These data were submitted to a repeated measures ANOVA with the within-subject factors phase (pre- vs. post-test) and hand (trained vs. untrained). For normal trials, the effects of phase, $F(1,10) = 71.98$, $p < .001$ and the Hand x Phase interaction were significant $F(1,10) = 10.61$, $p = .009$. The same was true for the Hand x Phase interaction for the trick trials, $F(1,10) = 7.56$, $p = .020$, indicating a "true" APA of the postural hand.

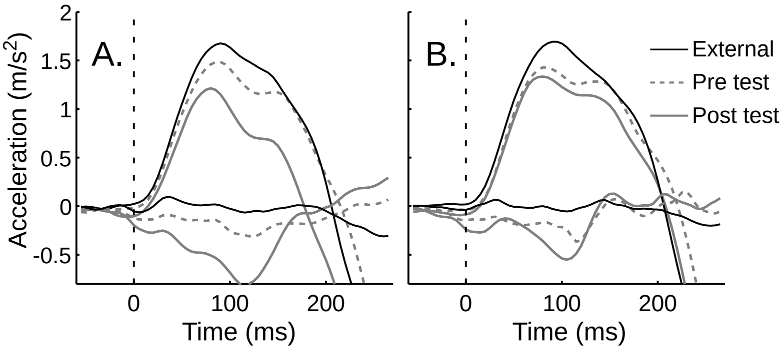

Figure 4.2: *Average acceleration traces for the trained (A) and untrained (B) hand for the age-matched controls during the pre- and post-test phases in the button press condition and in the external unloading condition.*

There were no differences between the three control participants who were trained on their non-dominant hand and those that who were trained on the dominant hand with the average reduction of upward perturbation being 0.22 m/s^2 vs. 0.2 m/s^2 (*SD* 0.086) respectively. We thus compared both unilateral and bilateral patients to the combined control group, irrespective whether the dominant or non-dominant hand was trained.

4.4.1 Cerebellar patients

Figure 4.3a shows the average acceleration traces of the trained hand for the patients with bilateral cerebellar damage. Immediately apparent is the lack of learning on both normal and trick trials. Indeed, the extent of the perturbation in the pre- and post- test phases of the button-press condition appeared to be equivalent to the external condition. Figure 4.4 shows the average acceleration measures for pre-test, post-test and learning phase for the three groups[2]. Again, the patients failed to exhibit any evidence of learning. They showed no differences between pre- and post-test phases and no change over the course of the learning trials. For statistical comparison between the controls and bilateral cerebellar

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[2] In the pre-test phase, one bilateral patient showed a substantially larger perturbation on button-press than on external trials (135%). I replaced the pre-test values for this patient with the perturbation value obtained on external trials, under the assumption that the latter value provides an estimate of the upper bound. For all other participants the perturbation in the button-press condition was equivalent or lower than in the external condition.

group, I conducted a repeated-measures ANOVA with the within-subject factor phase. The Phase x Group interaction was significant for normal trials, $F(1,15) = 15.44$, $p = .001$, and trick trials, $F(1,15) = 12.85$, $p = .003$. As a group, the bilateral cerebellar patients did not show a change from pre- to post-test on either the normal, $t(5) = 1.09$, $p = 0.325$ or the trick trials $t(5) = 1.62$, $p = .164$. Thus, the results indicate that the patients with bilateral cerebellar degeneration were unable to learn this bimanual coordination task.

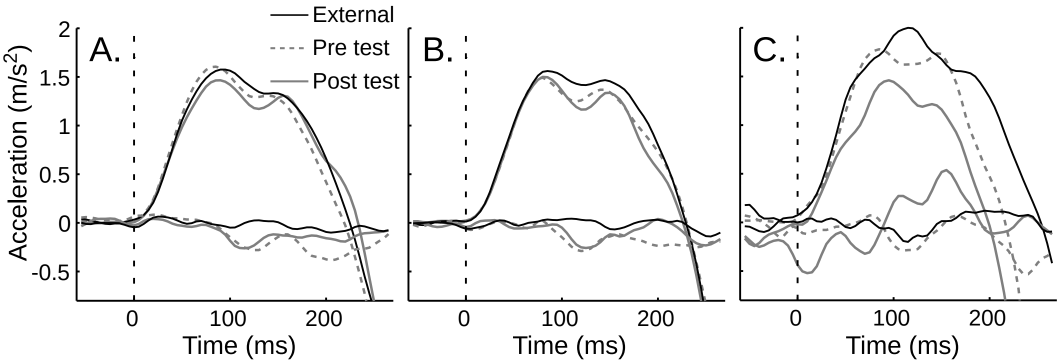

Figure 4.3: *Average acceleration traces for the trained hand of the bilateral degeneration patients (A), the unilateral patients (B) and the split-brain patient (C).*

The results for the unilateral cerebellar group (Figure 4.3b, Figure 4.4) are in accord with this hypothesis. The Phase x Group interaction was significant for normal trials, $F(1,6) = 13.53$, $p = .002$, and trick trials, $F(1,16) = 15.81$, $p = .001$, indicating that the patients differed statistically in their learning ability from the controls. The performance on trick trials confirms that this deficit cannot be attributed to altered reflex responses elicited by the perturbation on normal trials. As a group the unilateral cerebellar patients did not show significant differences in average acceleration between the pre- and post-test phases, both for normal and trick trials (both $t(6) < 1$). To access the amount of learning for each patient individually, I averaged the difference between pre- and post-test values across normal and trick trials. While the range the learning scores for control participants was -0.10 to -0.40m/s, all patients showed values of -0.05 or larger. Only patient EC demonstrated levels of learning that were comparable to the controls: -0.20 m/s^2. His lesion involved a small infarct to the right anterior lobe and lobus simplex, and he was nearly asymptomatic in the neurological evaluation.

4.4.2 Callosotomy patient

Before considering the learning effects, two points should be noted about the performance of the split-brain patient. First, the perturbations resulting from the unloading of the object were somewhat larger for the split-brain patient than that observed in the control participants (compare Figure 4.2a and Figure 4.3c). This patient is quite slender and the stiffness and inertia of her arm are quite low. Similar acceleration traces were found for a female control participant of comparable build. Second, despite the instructions, the split-brain patient frequently dropped her postural hand around the time of the button press. This problem was especially present at the beginning and end of the testing session, leading to the exclusion of 30% of her trials (see Procedure for criterion).

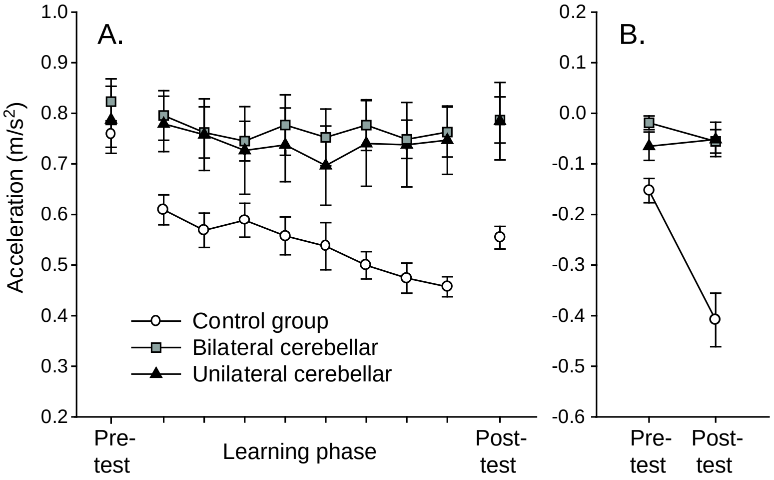

Figure 4.4: *Average acceleration in the time window from -25 to 125 ms on normal trials (A) and trick trials (B) for control and cerebellar patient groups. For the learning phase, each block of 24 trials is shown separately.*

Nonetheless, from the remaining data, it is evident that the callosotomy patient showed considerable learning (Figure 4.3c). There was a significant reduction in the size of the perturbation in the post-test phase, $t(25) = 3.485$, $p = .002$. She also exhibited a downward deflection on trick trials after training, although the size of this trick response was somewhat smaller than the response of the control participants, (-0.16 m/s^2 vs. -0.41 m/s^2; $SD = 0.18$).

In the training phase, the split brain patient showed a reduction from 0.94 m/s^2 to 0.73 m/s^2. The fit of a linear trend to the data in the learning phase revealed a significant downward slope $F(1, 125) = 4.72$, $p = .032$. The regression coefficient of -0.019 was comparable to that found in the control participants (Mean = -0.021, $SD = 0.013$).

4.5 Discussion

Consistent with previous reports (see Chapter 3, also Paulignan et al., 1989), the control participants in the current study were able to learn to make an anticipatory postural adjustment based on an arbitrary eliciting action. The most striking finding in the current study is the failure of the patients with cerebellar lesions to learn the anticipatory adjustment linked to a volitional, arbitrary movement. With the exception of one unilateral patient, none of the patients showed evidence of an improvement during the learning phase or a downward deflection during the trick-trials, which is the cleanest indication of an APA in the control participants.

Could the learning deficit be related to the demands of the button pressing action rather than an inability to coordinate the volitional and postural movements? It is possible that the button pressing task was not sufficiently automatized in cerebellar patients (Lang & Bastian, 2002), and thus required the patients to direct more attention to this movement rather than to its effects on the stability of the postural hand. Several arguments make this hypothesis unlikely. First, the button-press task only required a finger flexion; the hand of the participant was supported on the leg, stabilizing the finger right above the button. While the bilateral cerebellar group took longer time to depress the button (209 ms from contact to full depression) than healthy controls (121 ms) and also showed an increased variability (SD: 122 ms vs. 70 ms), neither of these differences was significant ($t(15) = 1.37$, $p = 0.19$, for the mean, and $t(15) < 1$, for the SD). Secondly, the characteristics of the button press action varied considerably among healthy controls, but did not correlated strongly with the size of the postural perturbation in the post-test ($r = 0.11$ for mean button press time and $r = 0.25$ for the variability). Third, and most importantly, the unilateral participants pressed the button with the contralesional, unimpaired hand. Nonetheless, they showed a similar learning deficit as found with the bilateral degeneration patients.

Despite some difficulties in performing the task, the callosotomy patient clearly demonstrated the ability to acquire a new APA in a bimanual task. This finding might seem at odds with previous studies that stress the importance of the corpus callosum in the acquisition of new bimanual motor behaviors (Andres et al., 1999; Franz et al., 2000; Preilowski, 1972). These studies, however, involved tasks that required the coordination of active movements of both hands. In the current study, the effects of learning are measured in the postural response of one hand, a behavior that may rely more strongly on subcortical mechanisms.

4.5.1 A neural network for postural adjustments during bimanual actions

Based on the current results the functional architecture underlying anticipatory postural adjustments in the unloading task (Massion et al., 1999; Viallet et al., 1992) can be further specified (Figure 4.5). The core points of the proposed system are the involvement of cortical motor areas contralateral to the postural hand, as well as a subcortical system, through which information can be exchanged without reliance on the corpus callosum.

What inferences can be made concerning the neural network involved in learning an anticipatory postural adjustment during indirect unloading? For learning to occur in the indirect unloading task, information associated with the button press must be available

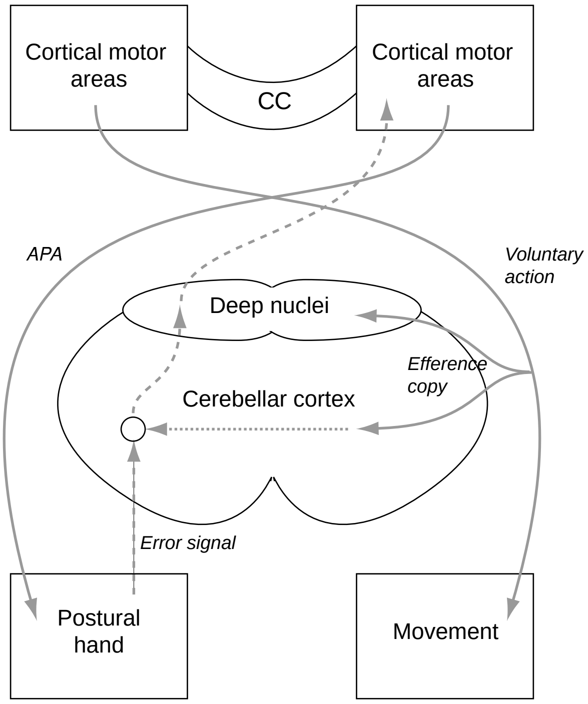

Figure 4.5: *Proposed functional architecture for the acquisition and control of anticipatory postural adjustments during bimanual coordination. The left motor cortex controls the prime mover, the right hand. An efference copy is sent via cortico-pontine fibers to the cerebellar cortex and deep nuclei. The induced perturbation leads to an error signal transmitted over the climbing fiber system to the cerebellum. The convergence of these signals in the cerebellar cortex, and perhaps also in the deep nuclei (not shown) provides the inputs for synaptic plasticity. Parallel fibers spanning the midline of the cerebellum might provide one possible mechanism in which information from the left and right side of the body are integrated (dotted line, see text for alternative possibilities). Cerebellar-thalamo-cortical projections to the right motor cortex lead to the expression of an APA. The contralateral basal ganglia and SMA are included in the original model proposed by Maisson (1999), but are not shown here, given that their contribution is not addressed in the current study.*

to neural areas involved in control of the APA. The current results show that learning is present in a split-brain patient. This suggests that the transmission of the button press information can occur over non-callosal fibers. Since I did not control for fixation in this task, in principle it is possible for visual information about the button press to reach the hemisphere contralateral to the postural hand. It is unlikely, however, that this information would have been sufficient to support learning. A previous study with the same paradigm (Chapter 3) showed that young, neurologically normal individuals fail to acquire an APA based on visual or proprioceptive information alone.

The results also indicate a critical role for the cerebellum in the learning process. The cerebellum has been shown to be involved in many aspects of motor learning, for example in sequence learning (Hallett & Grafman, 1997; Seitz, Roland, Bohm, Greitz, & Stone-Elander, 1990), tracking of a pursuit rotor (Grafton, Mazziotta, Presty, Friston, & et al., 1992), and the adaptation to a new visual (Gauthier, Hofferer, Hoyt, & Stark, 1979; Martin, Keating, Goodkin, Bastian, & Thach, 1996) or dynamic context (Shadmehr & Holcomb, 1997). This study extends the domain of cerebellar learning, providing the first demonstration that the integrity of the cerebellum is necessary for the acquisition of a new intermanual coordination task.

How could intermanual coordination be supported by the cerebellum? It is likely that the perturbation to the postural hand after unloading sends an errorsignal over climbing fibers into the ipsilateral cerebellum, akin to the neural signals observed during retinal slip (Simpson & Alley, 1974) or unexpected or aversive sensory information (Horn, Van Kan, & Gibson, 1996; Sears & Steinmetz, 1991). This error signal must be associated with information about the voluntary action. I assume that the signals led to plastisity in the hemisphere of the cerebellum ipsilateral to the postural hand. Such lateralization of learning is consistent with the fact the acquisition of an APA is hand-specific and the transfer to the other hand is limited (Chapter 3, Ioffe, Massion, Gantchev, Dufosse, & Kulikov, 1996).

The ipsilateral cerebellum thus needs access to the information about the button-press action from the other hemisphere. Two possibilities for this transfer exit. First, descending cortical signals may project, via cortico-pontine fibers, not only to the contralateral cerebellar hemisphere, but also to the ipsilateral cerebellar hemisphere. While the prefrontal, motor and parietal origins of cerebellar inputs have been recently mapped (Middleton & Strick, 2000), no information to my knowledge is available about degree of lateralization of these inputs (with the exception of visual inputs that show some ipsilateral projections, see Mower, Gibson, Robinson, Stein, & Glickstein, 1980).

Alternatively, the information about the upcoming action may be transmitted by the parallel fiber system within the cerebellum. Although the functional connectivity provided by parallel fiber beams is still a matter of debate (e.g. Bower, 2002), the beams could potentially transmit information across the midline of the cerebellum to connect the innermost cerebellar nuclei (Thach, Goodkin, & Keating, 1992). One way to evaluate these hypotheses would be to test the unilateral patients with their unimpaired, contralesional hand as the postural hand. While the ipsilateral input idea would predict that the acquisition of an APA should be possible, the parallel fiber hypothesis would predict an impairment since the damaged, ipsilesional side would be involved in trans-cerebellar transmission. Computational theories on cerebellar learning (e.g. Mauk & Donegan, 1997), based on the Marr-Albus hypothesis (Albus, 1971; Marr, 1969), would hold that learning mechanisms operate within both the cerebellar cortex and deep cerebellar nuclei.

Through ascending fibers, the output of the nuclei could shape the motor response generated in the contralateral cerebral hemisphere. In the case of the unloading task, information on the scaling and timing of the APA would be conveyed. The cerebellar output could also, however, influence the postural hand by way of descending fibers or through its influence on subcortical structures that are part of the extrapyramidal system (not shown in Figure 4.5).

It is likely that plastic changes also occur outside the cerebellum after extended practice. Lesions to the cerebellum did not reduce the size of the APA for natural unloading (see Chapter 2), a response acquired during childhood. However, even for overlearned behaviors, the cerebellum still may have a role in flexibly adjusting the responses to changes in the environment. This is congruent with the idea that the cerebellum provides a internal model of body-environment interaction (Haruno, Wolpert, & Kawato, 2001; Miall & Wolpert, 1996; Wolpert & Kawato, 1998; Wolpert, Miall, & Kawato, 1998).

The proposed model makes a number of critical predictions. One regards the activity of the cerebellar cortex during the learning of a new postural response in the bimanual context. The cerebellar cortex should be very active early in learning and slowly decrease, congruent with the idea that the error signal and resulting synaptic changes in the cerebellar cortex are the main physiological events for learning. This activity is expected to primarily occur in the cerebellar hemisphere ipsilateral to the postural hand. In contrast, the output signal from the cerebellum should increase during learning. This signal should carry information about the onset and size of the APA. Specifically, similar actions that do not elicit an APA should not lead to comparable activity. Thus, the output of the cerebellum would reflect the learned association between the action and expected perturbation. It should reflect the state of the body and the world, and would help the motor cortical areas to deal flexibly with new motor tasks and to integrate actions across different parts of the body.

Appendix A

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Appendix B

Inverse dynamics with the Phantom 3.0 system

B.1 Motivation

In a series of experiments, we test the properties of the human motor system. In particular, we are interested in how humans respond to expected or unexpected perturbation of the elbow joint. We apply forces in the vertical direction to the hand of a human subject, using a Phantom 3.0 (SensAble Technologies) system. A splint constrains the movement to the elbow joint, preventing any wrist- or finger movement.

The Phantom system provides measures of the force applied to the hand (F_{ex}) and the acceleration ($\ddot{x}$) of the hand of the human subject. From this we should be able to compute the force generated by the subject itself (F_{in}). In particular:

$$F_{in} = m\ddot{x} - F_{ex} \tag{B.1}$$

Inverse dynamics is a simple and powerful method to compare the output of the motor system under different perturbation conditions. It is important to find a way to estimate the inertia (m) of the imaginary point mass at the pivot-point, the connection between the phantom arm and the hand of the human subject. The inertia is likely to be a function of the phantom arm itself, the direction of the perturbation and the properties of the forearm attached to it.

Before estimating the inertia of the forearm and the forces generated by the participants, I decided to test Equation B.1 in the phantom system alone. If one attaches a weight to the phantom arm, the observed acceleration should be proportional to the force applied to the endpoint of the arm. The following experiment is targeted at investigating this question with a perturbation that is relatively similar to the perturbation used in the experiments involving human subjects.

B.2 Method

I attached a weight of known mass to the end of the arm of a Phantom 3.0. A program then simulated an elastic spring with a spring constant of $90\,N/m$. Given a certain position x and an equilibrium point p of the phantom arm at time t, the output was

$$F_{spring} = -(x-p)\,90\,\frac{N}{m} \tag{B.2}$$

When attaching a certain mass to the arm of the phantom, the system held the mass, applying the opposite of the gravitational force. After this equilibrium state is reached, the phantom provides a measurement of the equilibrium force (F_{equi}). A perturbation was then applied to the weight. The force was applied in vertical direction, and added to the force generated by the simulated spring following Equation B.2. The perturbation was composed of a half-period of a sinusoidal force pulse.

$$F_{perturb}(t) = 8\;N\;\sin(2\pi t\omega); \quad 0 < t < \frac{1}{2\omega} \tag{B.3}$$

I tested different weights at 5 different speed of perturbation $\omega = \{7,6,5,4,3\;Hz\}$. Each weight and perturbation speed was repeated 10 times. The average resultant force applied to the object ($F_{ex} = F_{spring} + F_{perturb}$) can be seen in Figure B.1. Position and force traces were recorded at a sampling rate at 500 Hz. I differentiated the position-trace numerically and the resultant acceleration trace was slightly smoothed with a Gaussian kernel of 1 ms SD (more on how the calculation of the acceleration might influence the results in the following section).

B.3 Results

Examples of an average force and acceleration trace with a weight of 200 g can be seen in Figure B.1. The measured acceleration profiles show some peculiarities. First, the acceleration begins before a force is applied. This is indeed an artifact of filtering; this effect is not present in unfiltered data. Second, the acceleration shows an initial spike in the first 10 ms. Whether this spike is an artifact of the way position is measured or if it is related to initial slack in the system, is unknown. Most worrisome for the inverse dynamics, however, is the fact that the peak of acceleration seems to be time-shifted forward, such that it precedes the peak of the force trace. This time shift can be seen more clearly, when force and acceleration are plotted against each other (Figure B.2). The time-shifted acceleration trace manifests itself in the ellipsoid shape of the curve. Formula 1 would have resulted in a single line.

The reason for this time shift is currently unclear. The artifact does not depend on sampling rate: I replicated the same results with sampling rates of 1000 Hz and 200 Hz, which leaves the results qualitatively unchanged. Filtering of the acceleration curves is not

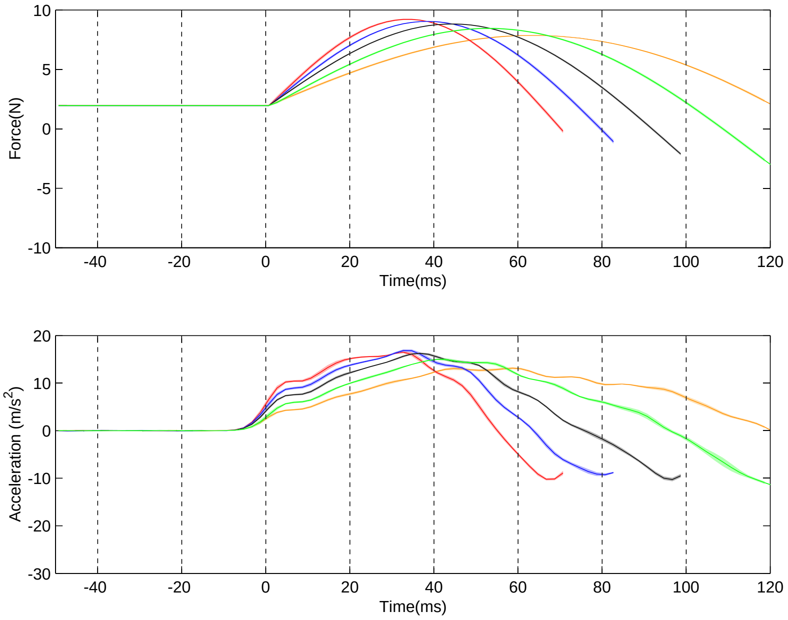

Figure B.1: *Average force (upper panel) and acceleration traces (lower panel) measured by the Phantom with a weight of 200 g attached to the endpoint of the arm. The perturbation started at 0 ms. Shaded areas around the traces indicate* ±1 SD *of 10 repetitions.*

the reason for the miss-alignment either, because the filter did not induce a time shift. The same miss-alignment can be seen in unfiltered data.

It turns out that for most weights and perturbation the force and acceleration curves can be realigned by shifting the acceleration back by 10 ms. With the present example this led to a satisfactory linear relationship between force and acceleration (see Figure B.3). The amount of time shift necessary to account for the artifacts might differ with differing weight and might be smaller with lower weights. This, however is difficult to access quantitatively from the current data set.

With the time-shifted acceleration trace, I can calculate the inertia of the phantom arm and the attached weight. Because both the force and acceleration were measured with noise, a linear regression would give different results for m, depending on whether force or acceleration is used as the regressor. I therefor calculated the first principal component ($\vec{v}$) of the force-acceleration data for each trial for the duration of the perturbation.

$$m_{intertia} = v_1/v_2; \tag{B.4}$$

This estimate can be compared to the actual weight of the attached object. Furthermore, the Phantom device provided another estimate of the weight of the object: the force the phantom measured when the object was held at equilibrium before the start of the perturbation. Figure B.4 shows both measures. The weight inferred from the force at equilibrium

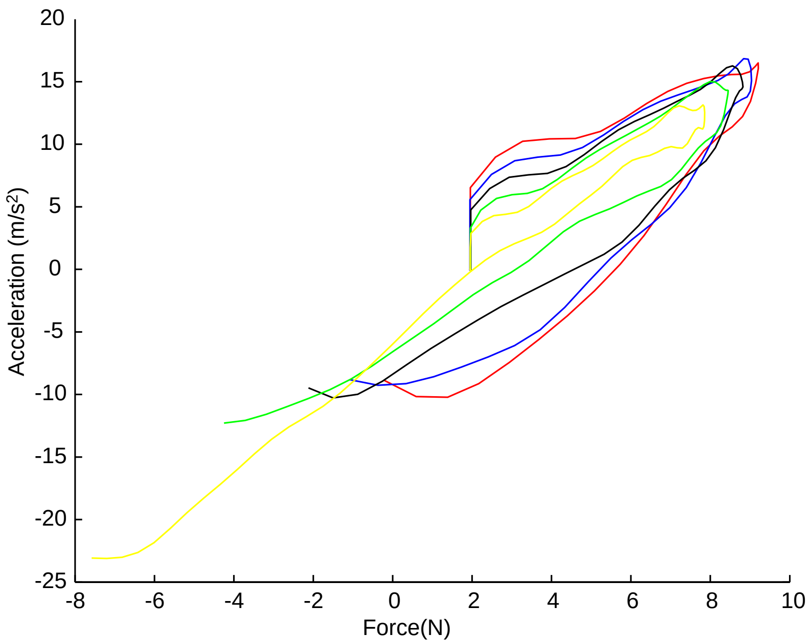

Figure B.2: *Force-acceleration plot of the data in Figure B.1.*

(F_{equi}) is rather reliable and an accurate representation of the actual weight.

While the inertia increases linearly with weight, it is on average 275 g higher than the weight of the object. The distance between the two curves seems to increase slightly with increasing weight. Also, there were some irregularities in the estimate of the inertia. Across the 10 trials and 5 speeds I achieved very consistent measures, the SD was very small. I suspect that the the way the weight was attached to the phantom arm may have played a major role here. The weights were not attached to the thimble, but taped on the side of the lower arm. This might have resulted in some cases in an unbalanced weight-distribution, which likely influenced the inertia of the arm. In more rigorous tests, the weight should be attached to the endpoint of the arm.

B.4 Conclusions

The current experiment with dead weights indicates that great care has to be taken when one wants to infer the inverse dynamics of a joint attached to a Phantom arm. The inertia attributable to the Phantom arm itself may exceed the value given in the technical documentation (150 g). However, the biggest problem seems to be a forward time-shift in the position signal from the phantom arm. This shift seems to occur whenever the position of the phantom arm is changing rapidly. When taking second derivatives it manifests itself in a peak of the acceleration in the first 10 ms and in a forward-shifted peak and zero crossing (see Figure B.1).

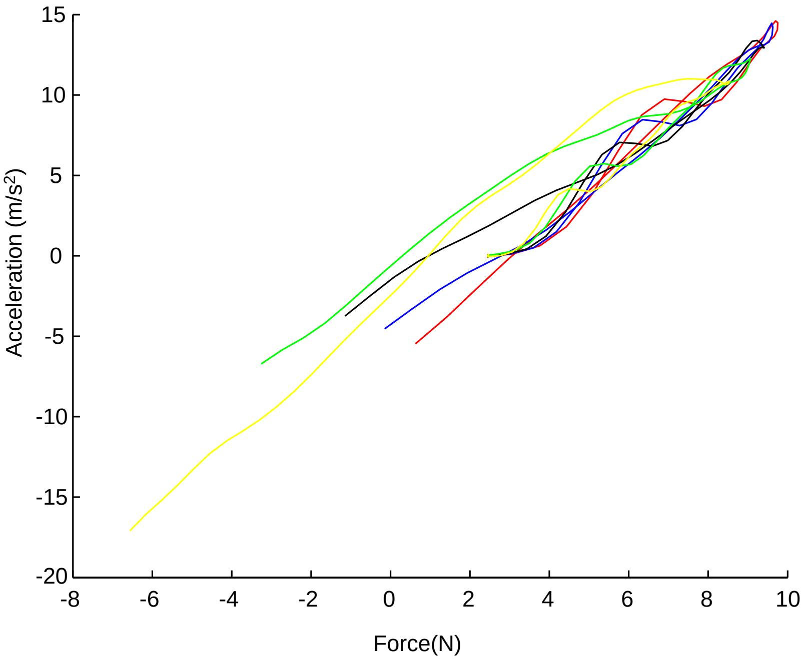

Figure B.3: *Force-acceleration plot of the data in Figure B.1. In this case the acceleration function was shifted 10 ms backwards in time.*

The reasons for this time-shift are unclear. One possibility is that slack in the system is acting like a spring between the arm and the weight. This allows the arm to accelerate, while the weight at the endpoint is not moving yet. I attached to weights directly to the phantom arm, so slack in the thimble itself could not have contributed to the result. However, slack in the internal mechanics of the system might be responsible.

The results are limited to the particular class of perturbations. It is very likely that perturbations in other directions, involving other joints of the phantom system, would yield different results. Before trying to infer the inverse dynamics of the human motor system from force and acceleration measures from the Phantom 3.0, it seems to be indicated to run a study with a similar perturbation with dead weights. Without knowing the behavior of the phantom system to the perturbation in question, any conclusions about human joint dynamics will likely be invalid.

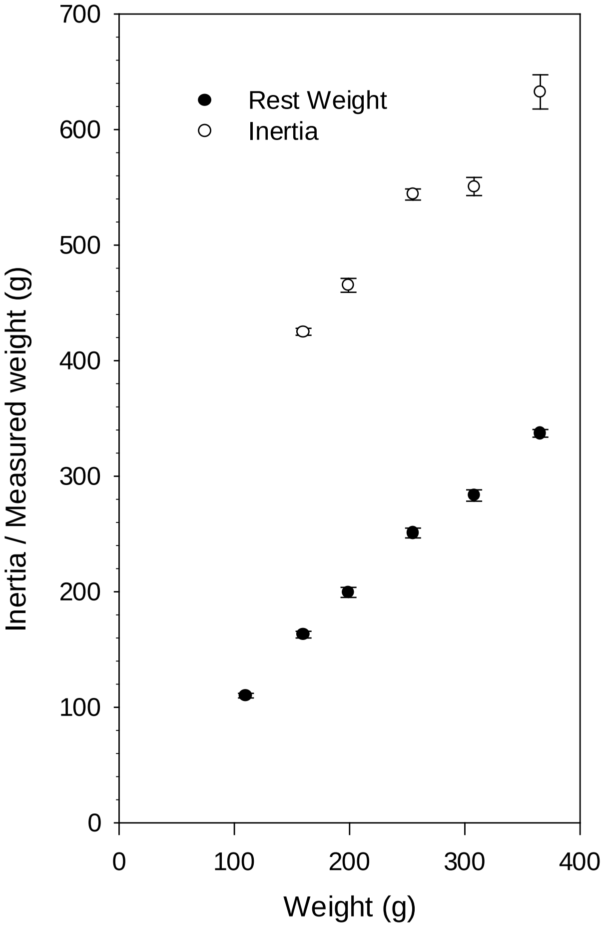

Figure B.4: *Average rest force and average estimated inertia of the arm for objects of different weights. Error-bars indicate* ±1 *SD of inter-trial variability.*