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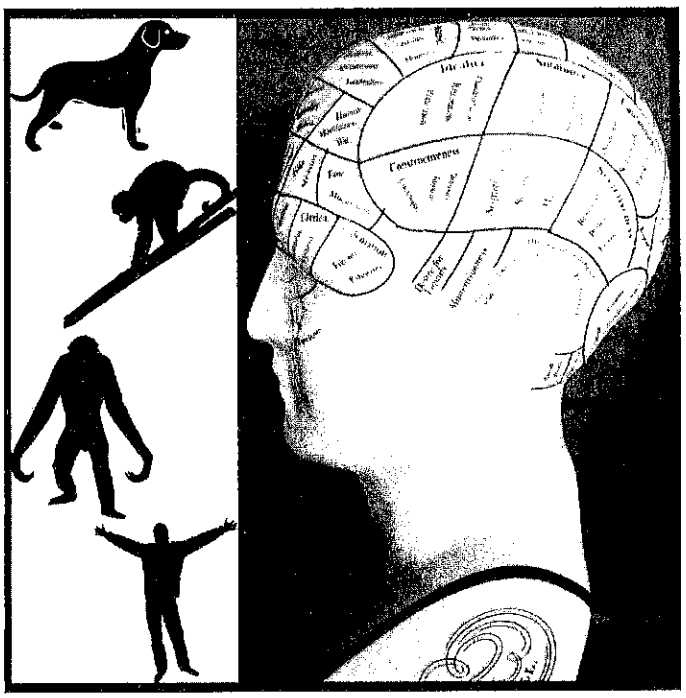

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8 Voluntary Movement Deficits of Eyes and Limbs: Neuroanatomy and Diagnosis

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Abstract

We present a systematic overview of voluntary eye and limb movement deficits that are caused by brain injury. The frontal lobes along with many other brain areas are believed to play a critical role in the voluntary movement of eyes and limbs. In particular, we explore the approximate locations of brain injury as well as the associated diagnostic procedures. The main findings of the review are that frontal regions are involved in saccades, smooth pursuit, grasping, unilateral action neglect, directional action neglect, anarchic hand disorder, utilization behavior, imitation behavior, motor perseverations, limb apraxia, imitation of meaningless gestures, limb apraxia (imitation of meaningful and meaningless gestures, tool and object use), but to a lesser extent in optic and kinaesthetic ataxia. Further, limb apraxia and anarchic hand disorder are the only voluntary movement deficits mainly associated with the left hemisphere of the brain. More fine-grained analysis may prove difficult due to limitations of findings and methods in lesion-symptom mapping. The overlapping networks for voluntary eye and limb action are evidence for a partially common module for eye-limb system control even if eye and limb movements are controlled by different brain regions.

1. Introduction

The motor system involves a functional division within the central nervous system. Voluntary movement deficit is a broad term that refers to many distinct disruptions in the voluntary motor system (also called pyramidal motor system) that are associated with various disorders such as reaching in optic ataxia and eye movements in visual search. Voluntary (endogenous, internally driven/evoked; endo-evoked) responses are made, for example, in response to arrows in the central visual field indicating likely target locations. Conversely, involuntary movement deficits, e.g. tremor, dystonia, and tics, are caused by injury in the involuntary movement system (also called extrapyramydal and cerebral systems) and are associated with movement disorders such as Parkinson's dementia. Involuntary (exogenous, externally driven/evoked, exo-evoked, automatic) responses are characterized by a reflexive response to salient stimuli, such

as abrupt movement in the peripheral visual field (e.g. Posner, 1980, 1989; Ebadi, 2005; Birian et al., 2006; see Blakemore et al., 2002 regarding awareness of the motor system). Voluntary control of the eyes and limbs involves a highly complex operation requiring coordinated interaction between various brain regions. For instance, simple flexing and extending of the fingers while the eyes are closed, evokes large brain activation in frontal and other areas in addition to primary motor and sensory areas (e.g. Filimon, 2010). Advanced neuroanatomical understanding of these mechanisms' function may help enhance the treatment and diagnosis of various neuropsychological deficits.

Neuropsychology concerns mainly higher order deficits, not primary deficits, with a few exceptions such as blindsight (Beaumont, 2008). Higher order functions refer to cortical operations such as organization, planning, decision-making, attention, etc. Areas such as the inferior parietal cortex are believed to operate as a sensorimotor interface (Mattingley et al., 1998). Conversely, primary order functions are characterized by lower brain functions such as color perception and movement execution. For example, the primary visual cortex, which the retinas of both eyes project elementary visual information to, is an area where this kind of primary function takes place. However, no clear-cut definition exists for the higher vs. lower order distinctions although our rough understanding is useful in the categorization of different disorders. Higher order deficits are especially interesting with respect to limbs and eyes since both are crucial for voluntary interaction with our environment. Many situations require the coordination of both involuntary and voluntary components of limb and eye movements, e.g. when using a wheelchair, where goals such as maintaining direction and remembering the route to the desired endpoint compete with various external sources of relevant information such as suddenly appearing-objects or pedestrians (e.g. Arai & Mardiyanto, 2011).

The main aim of this review is to describe and compare most voluntary motor deficits of eyes and limbs with respect to neuroanatomy as revealed by lesion-symptom mapping following various stroke-related neural injury and to outline neuropsychological assessment methods. The general neural mechanisms of voluntary movement are still not well understood for various reasons. For instance, some voluntary movement deficits are rare and can be difficult to diagnose (Birian et al., 2006). We aim to discuss and compare the neuroanatomical and diagnostic bases of different voluntary limb (i.e. action neglect, grasping, optic and kinaesthetic ataxia, anarchic hand disorder, utilization behavior, imitation behavior, motor preseverations, and limb aparaxia) and saccadic and smooth pursuit eye movement deficits. Precise understanding of diagnoses and neuroanatomy is important for the development of successful interventions. In particular, we explore how different brain areas are specialized for voluntary hand/limb and eye movements. This has not been addressed in previous reviews and studies on voluntary movement deficits following mainly stroke-related brain injury (see however a review by Filimon, 2010 on fMRI evidence). However, our aim is not

to evaluate the quality of the various neuroanatomical analyses, which vary considerably (e.g. Karnath & Perenin, 2005), but rather to provide an overview of voluntary movement deficits following brain injury. Most importantly, we hope to be able to pinpoint research fields where further research is urgently needed.

Our review consists of four main parts. First, we introduce the neuropsychology of voluntary limb and eye movement deficits; second, the neuroanatomy and diagnosis of voluntary eye movement deficits; third, the neuroanatomy and assessment of voluntary limb movement disorders; and lastly we discuss and summarize the main findings.

2. Saccadic and Smooth Pursuit Eye Movements

A relatively simple model of motor function in general can be provided by eye movements. Relative to other motor movements, eye movements are typically more easily measured and the movements have less degrees of freedom and are easier to analyze than other types of motor movement, since the number of muscles involved in eye movement generation is typically an order of magnitude lower than for other movement types. Saccades (see below) are probably the simplest motor actions made by organisms that are capable of moving their eyes independently of the trunk or the head in the first place, making them ideally suited to investigations of motor control. Many have therefore argued for the importance of understanding oculomotion, arguing that understanding eye movements may then inform the study of other motor movements in general. In fact the ease with which simple eye movement tests can be administered means that they can be the first indicators of degenerative motor disease while limb movement deficits are more likely to be addressed in a clinical assessment (Amador et al., 2006).

But a problem with research into specific motor disorders in the eye movement domain is that patients with sufficiently small and focal lesions to disrupt specific aspects of eye movement functioning are rare. Lesions are typically larger than this would require, and are, by their nature, indiscriminate in the damage they cause. Many insights have therefore been gained by investigating experimental lesions in non-human primates (see Tehovnik et al., 2000; Pierrot-Deiselligny, Rivaud et al., 1991; Pierrot-Deiselligny, Rosa et al., 1991, for review). In addition, low prevalence rates of lesions to particular regions of human cortex may prevent a clear taxonomy of distinct eye movement disorders. It is therefore important to keep in mind that not many deficits following neural damage are specific to eye movements. Overlap with other conditions contaminates precise diagnoses of eye movement disorders.

In what follows in this section, we describe the basic characteristics of the most studied eye (saccades, smooth pursuit) movement types and describe the paradigms typically used to study them before going on to describe the effects of neural damage upon eye movements (e.g. directional action neglect). Generally

speaking, in the field of eye movement research, more insights come from selective lesioning of the non-human primate brain than for voluntary limb movement deficits.

2.1. Saccades

Saccades are ballistic movements of the eye. Their vectors (or direction) and landing points are computed before they are executed, and once the command for the saccade has been made, relatively little changes can be made to the direction and landing point of the saccade (Leigh & Zee, 1999; Goldberg, 2000; Sparks, 2002). Saccades may be made either voluntarily or involuntarily (Kristjánsson, 2007). We can, in other words, plan to move our gaze to an item of interest in the field of vision. Such saccades are in that sense stimulus driven. Saccades can also occur involuntary in response to something that captures our attention. This is sometimes referred to as the visuo-motor grasp reflex (see e.g. Munoz & Everling, 2004; Fischer & Weber, 1993; see following discussion on the grasping reflex in section 3.1. as well in this context).

Furthermore, we can make saccades to locations in the visual field that have no stimulus. Such saccades are by their very nature internally generated. This difference between stimulus-driven and internally generated saccades is captured in a very popular paradigm for testing saccadic eye movements, the prosaccade/antisaccade paradigm (Antoniades et al., 2013; Kristjánsson, 2011; Munoz & Everling, 2004; Ross & Ross, 1980). This simple, yet surprisingly rich paradigm in terms of the information it yields, involves initial fixation on a central fixation point, and when the fixation point disappears, the task is either to make a saccade towards a stimulus that appears in the periphery on one side (prosaccade), or a saccade towards a mirror symmetric empty location on the other side of the fixation point (antisaccade). Hutton (2008) sums up what is probably the consensus in the literature, arguing that the paradigm involves a trade-off between bottom-up information such as target salience on the one hand and saccadic goals on the other. Observers may, in this way, often find their gaze drawn towards a location even if this goes against their intentions. Kristjánsson (2007) laid emphasis on *competition* between top-down and bottom-up influences in the generation of antisaccades, a view that accords well with the available data on the process (see below). The effects of neural damage upon antisaccade performance may therefore be very informative about neural control of saccadic eye movements, and by analogy, movement function. Large individual differences in antisaccade performance have been observed (Hutton, 2008) and many psychiatric and neurological disorders affect antisaccades in interesting ways (see below). One problem with antisaccade research is the lack of standardized methodology. This may be the reason for contradictory results in the literature (Antoniades et

al., 2013). Antoniades et al. argue that standardized protocols are needed for research using antisaccades and have proposed such a protocol, which many authors have started to use.

2.2. Neuroanatomy of Saccades

As mentioned before, voluntary saccadic eye movements are among the simplest movements that humans make. However, it would be an overstatement to say that the simplicity in execution is matched in some way by simplicity in brain circuitry guiding this motor function in humans, but at the same time the neuroanatomy of eye movements is rather well studied (for an overview see Leigh & Zee, 2011).

The key centers for control of saccade generation are the superior colliculi (SC) of the midbrain, the frontal (FEF) and supplementary (SEF) eye fields in the frontal lobes and the parietal eye fields (PEF) in the parietal cortex (situated on the horizontal portion of the intraparietal sulcus, in regions adjacent to the superior part of the angular gyrus and to the supramarginal gyrus). All these regions have strong connections with eye movement control centers in the brain stem.

The SC can locate a saccade target and generate a movement towards it on their own (Moschovakis, 1996), such as through the retinotectal pathway (Jóhannesson, Ásgeirsson & Kristjánsson, 2012; Jóhannesson & Kristjánsson, 2013; Williams, Azzopardi & Cowey, 1995) a phylogenetically old pathway that links the retina and SC directly without going through the cerebral cortex. The superior colliculi convey signals to movement generation centers in the brain stem (Cullen & Van Horn, 2011). However, input from saccade centers in the cerebral cortex complicate this picture. The frontal eye fields and the supplementary eye fields in the frontal lobes have direct input to the SC influencing its activity. The FEF are in turn fed information from V1, and the SC also interacts with the PEF.

The dorsolateral prefrontal cortex (dlPFC) also influences saccadic execution and interacts with the SC. Parietal areas also influence the process (in particular the parietal eye fields) strongly influencing saccade execution. This means that the SC does not handle saccade control in isolation. Additionally, regions in the Cerebellum are believed to play an important role in fine-tuning saccadic eye movements (Leigh & Zee, 2011). Roughly, the consensus in the literature appears to be that the FEF are involved in the control of voluntary saccades (Gaymard et al., 1998; Pierrot-Deseilligny et a., 2002). Even though saccades are generated by the brain stem, without cortical input (from the FEF or SC) saccades or not generated (Schiller, True & Conway, 1979, 1980). In non-human primates, the FEF and/or SC therefore appear to be necessary for eye movements. The FEF and SC contain neurons that provide a command signal for saccade generation if they

reach threshold for saccade generation. Note importantly, that the thresholds are flexible depending on task demands (Jantz, Watanabe, Everling & Munoz, 2013).

The PEF are thought to be particularly involved in generating stimulus driven saccades. The SEF are involved in initiating motor programs comprising multiple saccades or more complex motor programs, while the dorso-lateral prefrontal cortex (dlPFC) handles inhibition of reflexive saccades to external stimuli when they go against instruction and memory guided saccades – saccades that are to be made to remember locations rather than to visible stimuli. In addition Pierrot-Deisilligny et al. (2002) also propose that the dlPFC plays a critical role in the inhibition of reflexive saccades with the FEF subsequently generating the correct saccade in an antisaccade task. The dlPFC therefore plays an important role in tasks that have a memory component, in particular regarding tasks that involve memorizing instructions for saccades for later execution. Moreover, the cingulate eye field (in the anterior cingulate) is thought to manage motivation and the preparation of intentional saccades.

Evidence from functional magnetic resonance imaging supports this picture. Voluntary saccades cause greater FEF and parietal activity than reflexive saccades (Mort et al., 2003). The results of Bender et al. (2013) support the view that the FEF play a large role in the execution of internally generated saccades (see also, Reuter et al., 2010) while the parietal eye field is more involved with reflexive saccades.

One potentially important consideration arising from the results of Bender et al. (2013) is that since they used multivoxel pattern analysis, they argue that the *pattern* of activity is crucial for understanding neural control of eye movements, rather than control by specific regions. If this is true, lesion studies may be not nuanced enough to catch the critical neural patterns sufficiently well. It is important to keep this caveat in mind when the distribution of function is considered.

Eye movement related activity also occurs in the Cerebellum (Fukushima, Fukushima, Warabi & Barnes, 2013; Lekwuva & Barnes, 1996). The cerebellar dorsal vermis seems to be related to working memory functions during saccades (Fukushima et al., 2013).

2.3. Smooth Pursuit

To follow a moving visual stimulus with our eyes, or when we need to track a stationary stimulus while we ourselves move, we use smooth pursuit (SP) eye movements. SP eye movements have the curious characteristic that without a stimulus to be tracked, they cannot be made. Without a smoothly moving stimulus the movement would instead be a collection of jerky saccades (see e.g. Leigh & Zee, 1999; Chen et al., 1999; Krauzlis, 2004; Rashbass, 1961). Readers can easily try this for themselves by tracking their moving finger, and then trying to move their eyes in a similarly smooth manner across a stationary scene containing

no moving stimulus. The latter task will be impossible to perform in a smooth way, and the movement profile will contain a number of saccades.

The generation of SP eye movement requires correction for retinal slip (movement of stimuli across the retina) and also requires prediction of future locations of the stimulus to be tracked, because of inherent processing delays in the visual system. Smooth Pursuit has an onset latency of ~100-130 ms (Carl & Gellman, 1987). Typically the gain is 0.9-1.0 degrees, while corrective saccades are often seen for targets that move faster than 20°/sec (Leigh & Zee, 2011). Recent reviews of the neural control of saccades and pursuit indicate that there is a lot of overlap in the neural control systems for saccades and pursuit (Fukushima et al., 2013).

2.4. Neural Control of Smooth Pursuit

Perhaps the most important aspect that distinguishes neural control of smooth pursuit from saccades, is the involvement of regions related to motion processing in extrastriate cortex, not surprisingly, perhaps, since motion analysis is obviously necessary for SP. The MST area is critical in monkeys and an area roughly corresponding to V5 in humans. SP is also thought to be mediated by pathways connecting visual areas (for example involved in motion processing) to motor control areas in the Cerebellum (Krauzlis, 2004).

Smooth pursuit eye movements are controlled by a network of frontal and parietal regions (Heide, Kurzidim & Kömpf, 1996), which means that there is nevertheless considerable overlap in neural control between saccades and SP (Leigh & Zee, 2011; Krauzlis, 2004).

2.5. Disorders of Voluntary Oculomotor Function Following Lesions

2.5.1. Superior Colliculi

The superior colliculi (SC) of the midbrain connect strongly with brainstem reticular saccade generators and therefore play a critical role in saccade generation. The SC contains neurons whose activity peaks right before saccades are executed. Neurons in the deep layers of the SC, and the intermediate layers fire before eye movements, and the superficial layers have cells that give responses to stimuli that are the targets of upcoming eye movements (Mohler & Wurtz, 1976).

The functional neuroanatomy of the human SC is predominantly contralateral during saccade generation (Krebs et al., 2010; Sylvester, Josephs, Driver & Rees, 2007). Chemical deactivation or induced lesions of SC lead to impairment in the ability to voluntary move the eyes into the contralesional field (Hikosaka & Wurtz, 1986; Heilman et al. 1987). Pierrot-Deseilligny et al. (1991b) studied a patient with damage to only the right SC, revealing that the SC

play an important role in saccade initiation to contralateral items as well as saccade inhibition.

2.5.2. Frontal areas

The frontal eye field (FEF) connects strongly with brainstem saccade generation motor areas in the reticular formation (Leigh & Zee, 2011). It is well known how frontal areas serve an inhibitory function, which is useful for antisaccade generation. In a seminal study, Guitton et al. (1985) studied patients with FEF injury, reporting that such patients had great difficulty in suppressing reflexive saccades towards a stimulus during antisaccade task. They made erroneous saccades towards salient targets even though they were supposed to suppress these reflexive movements, and generate a saccade in the other direction. Note that these symptoms resemble limb apraxia (see section 3.9).

Rivaud et al. (1994) studied three patients with FEF brain injury. Their eye movement patterns indicated that the FEF plays a role in disengagement from fixation, the control of contralateral saccades and smooth pursuit. Additionally, damage to the FEF can have repercussions in effects upon other areas. Machado and Rafal (2004) argued that chronic damage to the FEF disrupts interactions between the colliculi and cortical control centers. This, in turn, causes hypoactivity in the contralesional SC and loss of strategic collicular control over central fixation. Henik, Rafal and Rhodes (1994) then reported that patients with prefrontal lesions show increased saccade latencies for the initiation of voluntary saccades (to blank locations) to the contralateral visual field during an antisaccade task. These symptoms resemble directional hand movement preservations (Heilman et al., 2008; see section 3.2 for further discussion).

The supplementary eye fields (SEF) are located slightly anterior and inferior to the frontal eye fields. The most notable deficit following damage to the SEF involves a difficulty in making preplanned sequences of saccades (Gaymard et al, 1993, 2003). These symptoms resemble optic ataxia (see section 3.3). Husain et al. (2003) studied a patient with a highly selective lesion of the SEF (with other regions intact). They found that the patient had difficulty with changing saccade direction from a previously learned instruction to meet newer task demands. They suggested that the SEF play a critical role in oculomotor control when there is response conflict. They also reported that the patient quickly corrected the mistakes made, suggesting that the SEF are not critical for error monitoring. Importantly, Husain et al. (2003) found that similar mistakes were not made on a comparable motor task indicating that the deficit was indeed eye movement specific. This result is consistent with neurophysiological studies on monkeys, which indicate that the SEF can flexibly map stimulus response relations (Chen & Wise, 1995).

Note that the potential role of the SEF may be of specific interest in the current review, since the SEF are part of the supplementary motor complex

(Krainik et al., *2001;* Nachev, Husin & Kennard, 2008) which has often been connected with action neglect (see section 3.2) of the current chapter.

In addition, lesions of the frontal eye fields cause impaired smooth pursuit (Leigh & Zee, 2011; Heide et al. 1996; Lekwuwa & Barnes, 1996) in particular a difficulty in generating pursuit into the ipsilateral visual field (Heide et al., 1996; Morrow & Sharpe, 1995; Krauzlis, 2004; see also MacAvoy et al., 1991 for converging evidence from lesioning studies of monkeys).

2.5.3. Dorso-Lateral Prefrontal Cortex (dlPFC)

According to Gaymard et al. (1998), the dlPFC is involved in the inhibition of reflexive saccades during an antisaccade task. Consistent with this, lesions of the dlPFC, cause impaired suppression of reflexive antisaccades (Condy et al., 2004). This accords well with the general claim that the dlPFC plays an important role in working memory function (Levy & Goldman-Rakic, 2000). The available evidence suggests that the dlPFC are involved in maintaining the required task in memory.

2.5.4. Parietal lobe

Unilateral neglect, or neglect for short, is a multimodal neuropsychological syndrome that can be described as a failure to respond and attend to objects on or to the contralesional side. It cannot be explained with primary motor and sensory impairments (Heilman et al., 1987; Saevarsson, Halsband & Kristjánsson, 2011). Neglect can be divided into output (i.e. action neglect) and input (i.e. perception) neglect. The disorder often follows parietal damage, commonly having a dramatic impact on eye movements to one side. Many different terms have been used to refer to this deficit such as directional action neglect (also called premotor neglect; Saevarsson, 2013a, b). The tight relationship between saccades and attention (Deubel & Schneider, 1996; Kowler et al., 1995; Kristjánsson et al., 2001), clearly suggests that the attentional problems that follow right parietal lesions should impact saccades and vice versa.

Eye movement latency increases both for saccades in ipsi- and contralateral space following right hemisphere damage, but typically there is a latency increase only into the contralateral field from left parietal damage (Pierrot-Deseilligny et al., 1991a). This asymmetry of symptoms is reminiscent of the well-known asymmetry in neglect (see e.g. Saevarsson, Halsband & Kristjánsson, 2011), reflected in the fact that neglect primarily occurs following right parietal lesions, but not following left parietal lesions.

Walker and Findlay (1996) studied saccadic performance in neglect patients, finding that the deficits in their saccade performance correlated overall rather well with their attentional dysfunction. For example, saccadic latency did

not increase with simultaneously presented bilateral targets as compared to unilateral targets, as is typically seen with normal observers, indicating that the contralesional stimulus did not capture attention as such stimuli will do for normal observers. Walker and Findlay suggest that this reflects that the ipsilesional SC is over-inhibited. Some of their patients also showed visual extinction in that they did not make saccades to the contralesional target when bilateral targets were presented. Note that the patients exhibited normal speed-ups in saccade latency with a temporal gap between fixation offset and target onset (a normal "gap-effect" in other words, Kristjánsson, 2011).

Sharpe, Cheng and Eizenmann (2011) argued that parietal lobe lesions caused impaired suppression of reflexive saccades and impaired generation of antisaccades through a disconnection between parietal lobe and frontal lobe oculomotor areas (such as the FEF).

Parietal eye movement areas connect with the superior coliculli. Gaymard et al. (2003) showed how the lateral intraparietal area (LIP) contributes to saccade generation through its role in spatial attentional capture. Parieteo-tectal nerve fibers are involved in an online signal for triggering reflexive saccades to salient stimuli (Rafal, 1991; see discussion in Jóhannesson, Ásgeirsson & Kristjánsson, 2012). Damage to parieto-tectal neural pathways severely affects performance accuracy in an unpredictable landing point paradigm driven by unpredictable salient stimuli. Note importantly, that lesions in parietal areas have a larger effect on saccadic eye movements if they occur in the right than the left hemisphere (Lekwuva & Barnes, 1996). Again, this accords well with findings on neglect. Heide, et al. (1995) studied patients with parietal lesions using a double-step saccade stimulus. They found that if the stimulus first jumped into the contralesional hemifield and then into the ipsilesional one, observers could not make an accurate saccade to the target even though it was in their *non*-affected hemifield. This result suggests that parietal areas are involved in calculating saccade amplitude in a dynamic way.

Parietal lesions can have a devastating effect on smooth pursuit. This is, in particular, likely for lesions that have some overlap with extrastriate motion processing areas that are nearby in the cortex (Heide et al., 1996). Some evidence also suggests that area V5 (the analogue of MT/MST in monkeys) is critical for SP, which is perhaps not surprising given the role of these mechanisms in motion perception (Krauzlis, 2004).

2.6. Cerebellum

Evidence from Monkeys

The cerebellum has direct neural projections onto brainstem generation centers (Bötzel, Rottach & Büttner, 1993; Robinson & Fuchs, 2001). The cerebellar dorsal vermis is involved in working memory related activity (Fukushima

et al., 2013) whereas the FEF and cerebellar areas are involved in movement preparation (Fukushima et al., 2013; Lekwuva & Barnes, 1996).

Importantly, the cerebellum also makes connections to cerebral saccade centers (Filippoulos, Eggert & Straube, 2013). The results of Barash et al. (1999) indicate that the cerebellum is involved in moment to moment recalibration such as in saccadic adaptation tasks (He & Kowler, 1989). Monkeys with damage to the posterior vermi (or oculomotor vermis) of the cerebellum showed hypometria and a permanent lack of short-term adaptation (Yamada & Noda, 1987). In fact the literature strongly indicates that lesions to the posterior vermis cause dysmetria (i.e. saccades that are shorter than the task requires).

2.6.1. Other results from cerebellar lesions in humans

Filippopulos et al. (2013) studied the role of the cerebellum in eye movements in 24 patients with cerebellar lesions. These patients showed saccades that were hypometric, had longer latencies, and exhibited errors of suppression in a memory guided saccade task. Lesions at various sites of the cerebellum (e.g. dorsal vermis or the Floccules) cause disorders of SP mainly of pursuit of targets moving in the ipsilesional direction of the hemifield.

Rambold et al. (2002) reported that the ventral paraflocculus of the cerebellum is critical for control of SP. The cerebellar vermis also plays an important role in SP; damage to the vermis harms the accuracy of pursuit initiation (Takagi, Zee & Tamargo, 2000). Damage to the cerebellar vermis may affect the trajectories of SP and saccades through impaired acceleration and deceleration. These findings are consistent with the proposal that the cerebellum may fine-tune the commands for SP, based on feedback (Krauzlis, 2004).

3. The Neuroanatomy and Assessment of Voluntary Limb Deficits

3.1. Grasping

Grasping reflex disorders are found in less than 10% of brain-injured patients in response to tactile stimulation of their affected hands and visual presentation of stimuli. Such disorders involve catching hold of a stimulus object without any explicit intention to use it. Some patients are able to suppress the grasp reaction voluntarily. However, most patients use their healthy hand to loosen the grasp of the other hand. Improper grasping can be diagnosed by stroking a patient's palm in a gentle and repetitive way with an object such as a pen. The patient is instructed not to grasp the pen. De Renzi and Barbieri (1992) found grasping in 70% of patients with bilateral and unilateral anterior cingulate gyrus injury, but this was less prevalent following damage to the supplementary motor cortex. Grasping also occurred in 26% of patients with lesions of other frontal areas (the lateral motor and premotor areas). Hemispheric asymmetry of grasping has not

been observed, however. Foot grasping has also been described as the flexion of toes in response to touching the sole, without movement of the stimulus. Moreover, five subvarieties of grasping (i.e. closing reaction, final grip, trap reaction, magnet reaction, and instinctive grouping) have been differentiated. Their neuroanatomical substrates have been specified neither for foot grasping nor for the subforms of grasping (De Renzi & Barbieri, 1992).

3.2. Action neglect

Action neglect is one form of unilateral neglect (see discussion in section 2.5.4) and can be explained by the lack of correct behavior or responses (e.g. in contrast to apraxia). Action neglect can be divided roughly into two main forms: motor and premotor neglect. Unilateral action neglect (also known as motor neglect, intentional motor disorder, intentional neglect, etc.; e.g. Mark, 1996) has been described as an underutilization of one side of the body without significant loss of strength, sensibility, or reflexes (Laplane & Degos, 1983). Common behavioral symptoms are, for instance, use of the ipsilesional hand when use of the other hand would be more convenient and appropriate, and difficulties using the affected limb in bimanual tasks such as clapping or opening a bottle. A subform of motor neglect called motor extinction has also been described. In short, it is detected when unimanual and bimanual limb movements are compared, and the contralesional limb shows significiantly poorer performance than the ipsilesional limb in bimanual tasks as opposed to unimanual tasks (Saevarsson, 2013a). Diagnosis is based on observing situations where the use of the contralesional hand would be more appropriate and on requesting patients to perform tasks that are normally performed with both hands, such as opening a bottle. The neuroanatomical injury most commonly believed to cause motor neglect is right unilateral damage to the frontal and/or parietal lobes, but subcortical brain injury is also connected to unilateral action neglect. Similar injury to the left side of the brain has also been reported to cause the affliction. The large inconsistencies across various studies are a considerable problem, however (Saevarsson, 2013a).

Directional action neglect (also known under other terms such as premotor neglect) refers to the voluntary response bias in or to the contralesional space of a non-affected ipsilesional body part that can occur on both sides. Hand movements are most often studied (Saevarsson, 2013a) although other movements, such as eye movements (see section 2.5.4), have been explored (e.g. Butter et al., 1988). Several different subtypes of directional action neglect have been described. For instance: directional hypokinesia refers to when initiation of a movement to one side is markedly slowed; directional akinesia refers to an inability to generate voluntary movements to one side; directional bradykinesia involves abnormally slow movements to one side; and directional hypometria refers to abnormally small amplitudes of a movement to one side. The neuroanatomy of directional action neglect is a controversial issue. Lesions in almost all subparts of

the brain have been suspected to cause the deficit. Saevarsson (2013a) argues that right unilateral frontal and parietal lobe injury combined with subcortical brain injury is the most common cause of directional action neglect. Similar injuries on the left side of the brain have also been reported to cause this form of action neglect. It is unclear which brain injury causes subtypes of directional action neglect (e.g. Simon et al., 1995). Many different methods have been developed to assess directional action neglect. Best known is the verbal-manual landmark task approach. Patients are requested to estimate pre-bisected lines by indicating orally if they are bisected in the middle or not. The patients are then requested to bisect the same or a similar line manually. If patients perform markedly worse on the manual landmark task than the verbal landmark task they are categorized as suffering from directional action neglect as well as visual neglect. Furthermore, various reaching and pointing tasks have been developed where visual conditions are controlled (e.g. Saevarsson, 2013a, b; Saevarssson & Kristjánsson, 2013; Saevarsson et al., 2014; Mattingley & Driver, 1997).

3.3. Optic ataxia

Optic ataxia (also called visuomotor ataxia or visuomotor apraxia, Freund, 2001) refers to the condition in which patients are unable to use visual input to guide goal-directed hand movements precisely (Balint, 1909). Symptoms may include inexact and halting reaching movements to visual objects such as a pen held in front of the patient, in contrast to rapid and exact reaching to non-visual objects such as the tip of their nose or the center of their glabella. Optic ataxia tends to be less pronounced in central vision than in the periphery. Optic ataxia affects reaching movements of both hands although it can in some cases be stronger for the contralesional hand. Optic ataxia can be diagnosed by asking patients to touch their nose top with their index finger, and to watch and move a small object such as a pen, in front of them (Rossetti et al., 2005). The neuroanatomical injury that is believed to cause optic ataxia is believed to be in the parieto-occipital junction (bilaterally) and/or superior parietal lobe (Karnath & Perenin, 2005), as well as the posterior parietal cortex in both hemispheres (Freund, 2001; Rossetti et al., 2005).

3.4. Kinaesthetic ataxia

Kinaesthetic ataxia (also known as parietal hand syndrome) refers to a neuropsychological deficit characterizezed by involuntary changes in hand position. Additionally, patients do not perform voluntary movements when the limbs are out of their visual guidance. The disorder is believed to be caused by insufficient processing of afferent kinaesthetic signals. When movements are guided visually, patients' grasping and hand coordination are still clumsy and their gait is staggering. Kinaesthetic ataxia can be diagnosed by observation of involuntary

hand displacement when the patient's visual attention is distracted or when a patient is simply blindfolded while imitating a certain hand movement. Neuroanatomical injuries found to cause kinaesthetic ataxia involve contralateral lesions to the affected hand of the anterior parietal lobe (Freund, 1987), lateral thalamus, or fiber tracts connecting these nodes (Goldenberg, 2010).

3.5. Anarchic hand

Anarchic hand disorder refers to a hand that can perform complicated movements that are clearly goal-directed, but, importantly, unintended (Della Sala et al., 1994; Brion & Jedynak, 1972). The movements are not under voluntary control and may interfere with voluntary actions of the non-affected hand. Patients may claim that the affected hand is disobedient or has a will of its own. For example, patients frequently refer to the affected limb in the third person (Marchetti & Della Sala, 1998). Normally, the action symptoms can be characterized by pulling and seizing various objects (Goldenberg, 2010). For instance, the alien hand may seize a phone from the other hand or undo shirt buttons. Patients may even be woken up by the anarchic limb as it tries to choke them (Banks et al., 1989). Some studies indicate that voluntary movements of an anarchic hand are impaired, especially in the presence of distractors, whereas involuntary hand movements are relatively intact (Cantagallo et al., 2010). Controversially, Tanaka et al. (1996) claimed that anarchic hand syndrome is a form of complex grasping or groping. Currently, the term "alien hand" is often used synonymously with "anarchic hand" (e.g. Biran et al., 2006) and several other abnormal types of hand behavior (Tanaka et al., 1996), although it was originally used to refer to the feeling of non-belonging of one's own hand when it was held behind the patient's back (Brion & Jedynak, 1972; Marchetti & Salla, 1998). Anarchic hand disorder is diagnosed by clinical observation, bimanual tasks (e.g. eating with a fork and knife), and the patient's subjective complaints of their own limbs as alien to themselves (e.g. Bakheit et al., 2013; Brainin et al., 2008). The neuroanatomical injury that typically causes anarchic hand syndrome in its most dramatic form is normally found in the corpus callosum, contralateral left superior, and medial frontal lobe (in particular the supplementary motor area; Birian et al., 2006; Cantagallo et al., 2010; Coulthard et al., 2007; Marchetti & Della Sala, 1998). Injury to the parietal lobe and thalamic nuclei accompanied by sensory loss has been found to cause a variant of the affliction (see Birian et al., 2006 for an overview).

3.6. Utilization behavior

Utilization behavior is characterized by a tendency to grasp with both hands and apply objects that are present within reaching distance in a way that is inappropriate for the situation but not the object (Lhermitte, 1983; Lhermitte et al., 1986). For instance, when sitting in front of a plate, holding a knife and fork,

patients may imitate gestures of eating. Clinical diagnosis of utilization behavior can be affected by enhanced suggestibility of brain-injured patients and it is therefore important that the patients are not aware of the purpose of the testing. Interesting objects (e.g. hourglass, newspaper, game pieces, pen and paper, mobile phone, parts of a brain model, comb, etc.) are placed on the side of a table where a patient is sitting while engaged in unrelated testing or conversation. Their spontaneous actions are then observed. If the patients use the objects, the examiner may ask why and the patient may claim that the examiner handed the objects to them and they therefore felt they should use them. The examiner may ask the patient not to use them and then observe their behavior further (Shallice et al., 1989). The behavior is not inhibited by verbal commands when it is related to the grasping reflex and a result of injury in large diffuse bilateral or unilateral medial frontal lesions, and perhaps the head of the caudate nucleus (Archibald et al., 2001; Lhermitte, 1983; Mori & Yamadori, 1982; Motomura, 1990; see also De Rensi & Barbieri, 1992). Shallice et al. (1989) suggested a differentiation between two forms of utilization behavior: an incidental and induced form. Incidental utilization behavior occurs when the examiner does not make any special attempt to draw the patient's attention to objects placed on two ends of a desk. Induced utilization behavior takes place when the behavior is elicited by putting the objects in the patient's hands.

3.7. Imitation Behavior

Imitation behavior in patients is described as the imitation of actions such as gestures of the examiner or other people when patients are not instructed to do so. Imitation behavior is a subform of utilization behavior (Lhermitte et al., 1986). For instance, patients may repeat instructions or imitate the finger pointing of the examiner. A clear-cut command to stop the imitation can indeed stop it, but it will typically reoccur shortly. When patients are asked why they imitate others, they may claim that the examiner indirectly requested them to imitate him, or they may be surprised and say nothing (De Renzi et al., 1996). Clinical diagnosis is based on gestures, brief instructions, and clinical observation of spontaneous imitation behavior. The gestures are typically initiated without any explanation. The examiner performs various gestures in front of the patient such as hair stroking, yawning, and clapping. If the patient imitates the behavior, he or she is asked to stop. The examiner then performs other behaviors such as humming a tone, sighing, and saying "that is enough," to reconfirm the diagnosis (De Renzi et al., 1996). Neuroanatomical injury associated with imitation behavior normally occurs in bilateral medial and lateral frontal lobes as well as structures of the basal ganglia such as the caudate nucleus (De Renzi et al., 1996). This is at odds with the findings of Lhermitte et al. (1986) who pinpoint the bilateral and unilateral frontal lobe as well as lower mediobasal injury (i.e. thalamus, caudate nucleus, and internal capsule areas) for this affliction.

3.8. Motor Perseverations

Motor perseveration occurs when a patient continues to perform certain acts even if their intended purpose has been fulfilled. For instance, they may press a response button repetitively on their left hand with their right hand although only one press is required (directional perseverations; Heilman et al., 2008) or patients may spend a long time washing their hands although they are already clean. When patients are asked about their motor perseverations they describe them as compulsive and unintentional, or they may rationalize them with plausible motivations, such as difficulties in seeing items when crossing out letters or other items on a neglect task. Motor perseverations are often confirmed with clinical observation in various settings. For instance, the deficit can be diagnosed by requesting a patient to cross out objects (e.g. in standard neglect task) with a pencil where they are observed for perseverate cancelations of the same items. Neuroanatomical injury related to motor perseveration has been found to be in uni- and bilateral areas of superior mesial frontal lobe, bilateral frontal lesions, basal ganglia, and additional diffuse brain injury (Goldberg, et al., 1981; Goldenberg, 2010; Sandson & Alberg, 1984). Consistent with this, Annoni et al. (1998) claim that any cerebral lesion at any location can lead to some form of perseverative behavior.

3.9. Limb Apraxia

Limb apraxia occurs when brain-injured patients fail to perform skilled and purposeful movements even when the ipsilesional hand shows completely intact skills (Steinthal, 1871; Liepmann, 1920). The affliction is commonly associated with aphasia although the severity of either disorder may differ within individuals. The deficit cannot be explained by ataxia, athetosis, ballismus, chorea, dystonia, muscular weakness, myoclonus, tremor, seizures, non-motor cognitive disorders (e.g. language comprehension, agnosia, and attention deficits), nor sensory deficits (e.g. hemianopia; Heilman & Rothi, 2012). Apraxia is a heterogeneous disorder characterized by a wide variety of movement errors. Different forms of apraxia have been proposed based on different kinds of errors (e.g. eye opening, speech, visuospatial functions, and facial movements). This section will only cover three forms of limb apraxia. Limb apraxia has been explained by three domains of actions (Goldenberg, 2010): (1) imitation of gestures, (2) performance of meaningful gestures, and (3) tool and object use.

Patients rarely complain that they are suffering from an apraxia of gesture (Rothi et al., 1990), and neither they nor their families are typically aware of it before formal clinical testing. Imitations of meaningful gestures are sometimes partially preserved since patients are able to understand the meaning of a gesture such as the "two-finger military salute" without being able to mimic the position

of the gesture itself. Patients are requested to imitate a demonstrated gesture with both their hands but their limb position for at least one hand is incorrect. If the patients do not understand the request, apraxia cannot be diagnosed. For instance, Heilman and Rothi (2012) and Goldenberg (1996, 2010) suggested various meaningful and meaningless finger and hand positions to evaluate imitation of gestures. For instance, patients were asked to mimic flipping a coin, using a toothbrush, waving goodbye, or putting their thumbs in their ears. Use of various tools and objects may fail because knowledge about the use of a tool or object may have disappeared (degraded semantic memory) or they may understand the use of the tool but are unable to perform the action (intentional motor deficit). For instance, a patient may try to cut bread by turning a knife upside down. Furthermore, problems can also start to appear when more complicated sequences of actions with objects and tools are evaluated, such as when patients are asked to prepare a meal (Hodges et al., 2000).

Neuroanatomy of limb apraxia: Impaired imitation of meaningless hand postures or gestures is associated with damage to the inferior parietal cortex in the left hemisphere, while disturbed imitation of meaningless finger stance is linked to inferior frontal (including the opercular portion) and precentral brain injury (i.e. motor cortex; Halsband et al., 2001; Goldenberg & Karnath, 2006) in the left hemisphere. Apraxia of meaningful gestures is associated with left hemisphere neural damage, particularly the inferior frontal cortex and underlying white matter (Goldenberg et al., 2007). Simple and multi-step tool and object use has been associated with injury to the parietal lobe of the left hemisphere. Studies have revealed no differences in neuroanatomical lesions between simple and multi-step tool and object apraxia (Goldenberg & Hagmann, 1998). The loss of knowledge about the use of tools or objects in association with a preserved ability to figure out possible functions has been related to bilateral temporal lobe brain injury (Hodges et al., 2000).

4. Discussion

Voluntary eye and limb movement defects are often associated with bilateral injury to frontal areas (e.g. Butter et al., 1988). However, voluntary movement deficits of eyes and limbs are related to various other brain injuries. Frontal brain injury is most commonly identified for voluntary limb and eye deficits, although the overlap is far from complete. The disorders are also associated with injury to parietal cortex, subcortical areas or white matter. This finding corroborates fMRI evidence that activation in the frontal and parietal cortex such as in the precuneus and frontal eye fields are part of the network for reaching and saccades (e.g. Filimon, 2010; Filimon et al., 2009). Apraxia and anarchic hand are the only voluntary motor deficits that were mainly associated with the left side of the brain, but not with right nor bilateral injury. Table 1 shows the main finding

of the review – how different brain regions are associated with voluntary movement disorders. More fine-grained comparison analyses of the neuroanatomy of the disorders than is presented in table 1 is not feasible since the diagnostic and lesion-symptom approaches as well as the number of studies on voluntary movement deficits vary greatly.

Deficits	Frontal lobe	Temporal lobe	Parietal lobe	Occipital lobe	Cerebellum	Subcortical areas / white matter	Limbic lobe
Saccades	LR		LR		LR	LR	
Smooth Pursuit	LR		LR	LR			
Grasping	LR						LR
Unilateral action neglect	LR		LR			LR	
Directional action neglect	LR		LR			LR	
Optic ataxia			LR	LR			
Kinaesthetic ataxia			LR			LR	
Anarchic hand	L						
Utilization behavior	LR					LR	
Imitation behavior	LR					LR	
Motor perseverations	LR					LR	
Limb apraxia: imitation of meaningless gestures	L						

Limb apraxia: imitation meaningful gestures	L				L
Limb apraxia: tool and object use		LR	L		

Table 1. *Comparison of different voluntary movement deficits of limbs and eyes with respect to different areas of the brain. L refers to left side and R to right side of the brain.*

The underlying neuroanatomical causes of deficits of voluntary eye and limb movement remain in many ways controversial. It is not possible to identify specific voluntary movement deficits based on the location of brain injury for various methodological reasons. For instance, lesion-symptom mapping procedures addressed in this review vary greatly in quality and sample size and it may be questionable to compare studies within and between certain neuropsychological deficits (e.g. Saevarsson et al., 2014). For example, the findings of De Renzi et al. (1996) and Lhermitte et al. (1986) reveal differences in the incidence of imitation and utilization behavior in frontal injured patients – probably because of different selection criteria. Furthermore, diagnoses of voluntary movement deficits can be challenging. Symptoms of different voluntary movement disorders may be confused with one another. For example, abnormal actions in neglect and optic ataxia as well as utilization behavior may look very similar because of shared clinical features and differing diagnostic methods (e.g. Saevarsson, 2013a, b; De Renzi et al., 1996). Neuroanatomical methods such as simple descriptions of brain injury, Damasio and Damasio (1989) lesion template method, or more advanced voxel-by-voxel lesion-symptom mapping methods (Rorden & Bett, 2000) vary greatly in terms of quality and approach. For instance, exact drawings of certain injuries is more informative than descriptions and may therefore be less prone to error.

Future studies will need to address voluntary motor disorders with more detailed assessment and neuroanatomy, and comparing them precisely with other voluntary movement deficits. Eye and limb deficits are similar in many respects. For instance, symptoms of erroneous eye saccades can resemble limb apraxia. Results indicating a common frontal involvement in most voluntary movement deficits call for a more systematic study of various voluntary movement defects with respect to neuroanatomy and therapy.