

**DEVELOPMENT AND DEGENERATION OF THE SENSORY CONTROL
OF REACH-TO-EAT BEHAVIOUR**

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Dedication

For Allen and Alexander

Thesis Abstract

The reach-to-eat movement, in which a hand is advanced towards a food item, shapes to grasp the food item, and withdrawals to place the food item into the mouth for eating, is a behaviour that is performed daily. The movement is controlled by two sensory systems, vision to guide hand advance and grasping, and somatosensation to guide hand withdrawal and mouth placement. The purpose of the present thesis was to examine how the sensory control of reaching-to-eat develops in infancy and degenerates following neurodegenerative disorder. The tight coupling of vision to hand advance and somatosensation to hand withdrawal has a developmental profile from six months to one year of age. That is, six-month-old infants rely on vision to advance their hand, grasp the target, and withdrawal the target to the mouth. By twelve months of age, infants display the adult pattern of coupling vision to hand advance and grasping. The tight coupling of vision to hand advance degenerates with basal ganglia disease, such that subjects with Parkinson's disease and Huntington's disease show an overreliance on vision to guide hand advance for grasping and hand withdrawal for mouth placement. The results of the thesis demonstrate that efficient use of sensory control to guide motor behaviour is an important aspect of development that is disrupted by neurodegenerative disease.

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**DEVELOPMENT AND DEGENERATION OF THE SENSORY CONTROL
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TABLE OF CONTENTS

Chapter 1: Introduction	1
Chapter 2: Development of rotational movements, hand shaping, and accuracy in advance and withdrawal for the reach-to-eat movement in human infants aged 6 to 12 months	59
Chapter 3: Development of visual and somatosensory attention of the reach-to-eat movement in human infants aged 6 to 12 months	112
Chapter 4: Drug treatment and familiar music aids an attention shift from vision to somatosensation in Parkinson's disease on the reach-to-eat task	163
Chapter 5: Proximal Movements Compensate for Distal Movement Impairments in a Reach-To-Eat Task in Huntington's Disease: New Insights into Motor Impairments in a Real-World Skill	204
Chapter 6: Discussion	242
Future Directions	285
Appendix	286

List of Tables

Chapter 1

Table 1. Descending pathways of the brain involved in reaching behaviour	15
Table 2. Skilled Reaching Rating Scale	35

Chapter 2

Table 1. Skilled Reaching Rating Scale	71
Table 2. Total number of reaches for each infant	72

Chapter 3

None

Chapter 4

Table 1. Parkinson's diseased subjects characteristics	169
--	-----

Chapter 5

Table 1. Huntington's disease subjects characteristics	209
Table 2. Movement element rating scale	213
Table 3. Behaviours that are abnormal in HD subjects	216

Chapter 6

None

List of Figures

Chapter 1

Figure 1. Diagram of the motor system	4
Figure 2. Diagram of the lobes of the cerebellum	8
Figure 3. The nuclei of the basal ganglia	10
Figure 4. The direct pathway of the basal ganglia	11
Figure 5. The indirect pathway of the basal ganglia	13
Figure 6. Diagram of the voluntary saccade system in humans	17
Figure 7. Diagram of myelination progression during prenatal and postnatal development	19
Figure 8. The direct and indirect pathways of the basal ganglia of the Parkinsonian brain	21
Figure 9. The direct and indirect pathways of the basal ganglia of the Huntington brain	23
Figure 10. Sensorimotor network underlying reaching-to-eat behaviour	25
Figure 11. Reaching task for infants	31
Figure 12. Reaching task for adults	32

Chapter 2

Figure 1. Reaching task for infants and adults	67
Figure 2. Skilled Reaching Rating Scale	76
Figure 3. I. Visual disengagement	78
Figure 4. Advance	80
Figure 5. Grasp	83
Figure 6. Withdrawal	85
Figure 7. Release	87
Figure 8. Representative kinematics of hand trajectory and velocity	89

Figure 9. Hand rotation	91
Figure 10. Hand use preference by infants	93

Chapter 3

Figure 1. Reaching task for infants and adults	120
Figure 2. Comparison of the automatic and manual methods for tracking hand and eye movements	129
Figure 3. Example photographs of digit shaping and grasps	131
Figure 4. Representative examples of the temporal coupling of hand and eye movements	135
Figure 5. Time to complete advance and withdrawal in infants	137
Figure 6. Time to complete engage-to-move and grasp-to-disengage for infants	139
Figure 7. Comparison of arm and eye measures for twelve-month-olds and adults	141
Figure 8. Proportion of grasp shapes in infancy	143
Figure 9. Proportion of grasp errors in infancy	144
Figure 10. Proportion of mouth placement errors in infancy	146

Chapter 4

Figure 1. Procedural timeline for the Parkinson's diseased subjects	169
Figure 2. Experimental set-up	172
Figure 3. Kinematic measurement of wrist and eye in Parkinson's diseased subjects and age-matched controls	174
Figure 4. Eye and hand measures for age-matched controls	178
Figure 5. Movement component score for age-matched controls	179
Figure 6. Duration of time to complete advance and withdrawal for subjects with Parkinson's disease	180

Figure 7. Duration of time to complete engage-to-move and grasp-to-disengage for subjects with Parkinson's disease	182
--	-----

Figure 8. Movement component score for subjects with Parkinson's disease	183
--	-----

Chapter 5

Figure 1. Experimental set-up	210
-------------------------------	-----

Figure 2. Superimposed images of an age-matched control and a subject with Huntington's disease	217
---	-----

Figure 3. Photographs of an age-matched control and a subject with Huntington's disease grasping	219
--	-----

Figure 4. Photographs of an age-matched control and a subject with Huntington's disease withdrawing food to mouth	220
---	-----

Figure 5. Photographs of an age-matched control and a subject with Huntington's disease returning hand to start position	221
--	-----

Figure 6. Movement element scores for age-matched controls and subjects with Huntington's disease	222
---	-----

Figure 7. Kinematic analysis of hand rotation	223
---	-----

Figure 8. Hand trajectories for an age-matched control, a mild, and an advanced Huntington's disease subject	224
--	-----

Chapter 6

Figure 1. Experimental set-up	248
-------------------------------	-----

Figure 2. Photographs of temporal coupling of hand and eye	249
--	-----

Figure 3. Duration of time for advance and withdrawal with vision and visual occlusion	251
--	-----

Figure 4. Experimental set-up for infants	254
---	-----

Figure 5. Photographs of visual fixation and disengagement in six- and twelve-month-old infants	256
---	-----

Figure 6. Representations of first mouth contacts at six-, nine-, and twelve-months-old	257
---	-----

Figure 7. Time for engage-to-move and grasp-to-disengage for six-, nine-, and twelve-months-old infants	258
Figure 8. Movement component score for six-, nine-, and twelve-months-old infants	259
Figure 9. Duration of time to complete engage-to-move and grasp-to-disengage for young and old adult controls and mild and advanced Parkinsonian subjects	263

List of Abbreviations

ANOVA	Analysis of Variance
D	Medications only
D+M	Medications and music
f/sec	Frames per second
Far	Touches skin distal to mouth first
HD	Huntington's disease
IREd	Infrared emitting diode
LED	Light emitting diode
Lips	Touches lips first
M	Music only
M1	Primary motor cortex
Near	Touches skin surrounding lips first
NT	No treatment
OAC	Age-matched older adult controls
OS	Overshoot
PD	Parkinson's disease
PMd	Dorsal premotor area
PMdc	Caudal aspect of dorsal premotor area
PMv	Ventral premotor area
PSSA	Parkinson's Society of Southern Alberta
RAS	Rhythmic Auditory Stimulation
S1	Primary somatosensory area
SMA	Supplementary motor area
SPSS	Statistical Package for the Social Sciences

SRRS	Skilled Reaching Rating Scale
Supi	Supination
T/R	Touch and release
UHDRS	Unified Huntington's Disease Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
US	Undershoot
YAC	Young adult controls

Chapter 1

Introduction

Introduction

On Movement and Reaching Behaviour

Reaching the hand towards an object to grasp and manipulate is a movement that each of us performs daily. Although a seemingly simple motor task, goal-directed reaching requires sensory information concerning object size, shape, and distance from the body (Milner & Goodale, 1995) to be transformed into muscle command signals to accurately reach the hand towards the object and shape the digits for grasping (Krakauer & Ghez, 2000). The end-goal of the movement determines which joints and muscles will be ‘selected’ to perform the movement (Krakauer et al., 2000). That is, if a person grasps a Cheerio™ to eat, the joints and muscles in the shoulder, arm, hand, and face will be activated rather than joints and muscles in the hips and legs (as would be required if kicking a soccer ball).

The ability to transform the sensory representation of a ‘small food item’ into the appropriate motor output command of ‘reach towards and grasp’ requires an interconnected network of areas in the brain and spinal cord (Ghez & Krakauer, 2000). In simplistic terms, visual information concerning the target (Cheerio™) enters the retina and is carried along the optic nerve to the occipital cortex. Characteristics of the target, such as size, shape, and colour, are sent via the ventral pathway from the occipital cortex to the temporal cortex to allow the object to be recognized as a Cheerio™. At the same time, the information is sent via the dorsal pathway from the occipital cortex to the parietal cortex to activate the “reaching for a small object” motor program. Once signalled to start reaching, the motor cortex and spinal cord

carry out the motor program of “reaching for a small target to place into the mouth for eating” (Prodoehl, Corcos, & Vaillancourt, 2009). The ability to select the appropriate motor output in response to a sensory event requires experience and learning (Krakauer et al., 2000) and the loss of this ability is often one of the first symptoms of neurodegenerative diseases of the motor system (Doan, Melvin, Whishaw, & Suchowersky, 2008).

Voluntary Movement Control Exists Throughout the Brain

Movements of the arm and hand are controlled by a series of structures in the brain and spinal cord and include such movements as tapping the fingers, reaching for objects, and sign language. To examine all movements of the arm and hand in a single thesis would be an arduous endeavour, thus the present thesis focuses on voluntary reaching behaviour, that is reaching a hand towards a target, grasping the target with the digits, and withdrawing the target to the mouth for eating.

Cortical areas of the brain involved in reaching behaviour. The motor system is comprised of several sub-cortices, as shown in Figure 1. The primary motor cortex (M1) lies on the precentral gyrus, rostral to the central sulcus. The pyramidal somata of layer V (output cells) are exceptionally large, and the granule somata of layer IV (input cells) are sparse, making M1 readily recognizable (Scheiber, 1999). The pyramidal neurons of layer V project to the motor neurons of the spinal cord to produce the desired motor response in the required muscles and tendons.

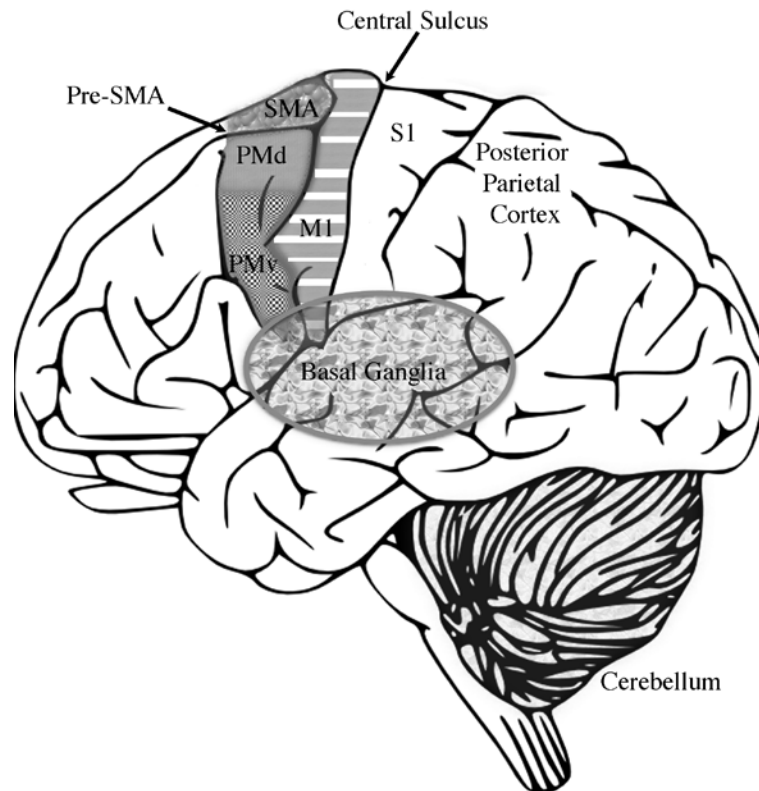


Figure 1. Diagram of the motor system. The cortical areas of the motor system are anterior to the central sulcus and are shaded in different patterns (M1: primary motor area, SMA: supplementary motor area, pre-SMA: pre-supplementary motor area, PMd: dorsal premotor cortex, PMv: ventral premotor cortex). The basal ganglia are located beneath the cortex, but its approximate location is indicated. The areas of primary somatosensory cortex (S1) and posterior parietal cortex (which project onto the motor cortices) are also noted.

Primary motor cortex (M1) integrates the inputs it receives from premotor areas, the cerebellum, the basal ganglia, and sensory areas of the brain and decomposes them into simple motor outputs, activating only those muscles required to drive the appropriate response. As such, gross electrical stimulation of M1 evokes a somatotopic map of the body with the face represented more laterally and arm and leg represented more medially (the motor homunculus; Graziano, 2006; Graziano, Aflalo, & Cooke, 2005; Stepniewska, Fang, & Kaas, 2005; Leyton & Sherrington, 1917; Penfield & Boldrey, 1937). In addition to organization by major body part, M1 also

contains a proximal-distal map of the body, with the distal parts of the arms, as well as the face and tongue, located caudally, and the proximal parts of the body located rostrally. It is of note that the somatotopic map of M1 is not subdivided into compacted sections, but rather the bodily representations are overlapping and intermixed, suggesting a vast organizational schema to coordinate muscles and joints (Donoghue, Leinhardt, & Sanes, 1992; Park, Belhaj-Saif, Gordon, & Cheney, 2001; Sanes & Schieber 2001; Schieber 2002; Crowe, Chafee, Averbeck, & Georgopoulos, 2004; Georgopoulos, Schwartz, & Kettner, 1986; Reina, Moran, & Schwartz, 2001).

Secondary motor cortices consist of the premotor cortex, which lies anterior to M1 and is comprised of a dorsal (PMd) and ventral (PMv) division, the supplementary motor area (SMA), which lies above the dorsal premotor cortex, and the pre-supplementary motor area (pre-SMA), which lies anterior to SMA (Picard & Strick, 1996; Picard & Strick, 2001; Graziano, 2006). Primary somatosensory cortex (S1), located on the post-central gyrus, and the posterior parietal cortex, located caudally to S1, are motor association areas.

The functions of many of the secondary motor areas complement that of M1. Dorsal premotor cortex plans the 'reaching' component of the reach-to-grasp movement (Wise, 1985; Prodoehl et al., 2009; Caminiti, Johnson, Galli, Ferranina, & Burnod, 1991; Crammond & Kalaska, 1996; Bauswein & Fromm, 1992; Hocherman & Wise 1991; Messier & Kalaska 2000), whereas ventral premotor cortex plans the 'grasping' component of the reach-to-grasp movement in response to external stimuli (Rizzolatti, Camarda, Fogassi, Gentilucci, Luppino, & Matelli, 1988; Prodoehl, Corcos, & Vaillancourt, 2009). Pre-supplementary motor area and supplementary

motor area play a role in the learning and selection of action sequences (Grezes & Decety, 2002; Tanji, 2001; Mushiake, Inase, & Tanji, 1990; Cunnington et al., 2002; Chen & Wise, 1996) and are involved in the production of internally generated and memory-guided motor responses (Cunnington, Windischberger, Deecke, & Moser, 2002). The posterior parietal cortex integrates somatosensory information about the location of the arm and hand from S1 and visual coordinates of the target from occipital cortex to create target coordinates for the reaching action (Gharbawie, Stepniewska, Qi, & Kaas, 2011).

The motor areas work together to produce the desired motor response. Neurons in posterior parietal cortex transform visual information about the location of the target in extrapersonal space into arm-centered coordinates and hand-centered coordinates. These coordinates are then sent to dorsal and ventral premotor cortex to activate the “reaching” and “grasping” motor programs, respectively. The supplementary motor area collects the information from the premotor cortices and plans the reach-to-grasp movement. Information concerning the muscle sequence is projected onto M1 to activate the necessary muscles (Weinrich, Wise, & Mauritz, 1984; Kurata, 1989; Tanji & Kurata, 1982; Wise, Weinrich, & Mauritz, 1986).

More recently, electrical stimulation of motor cortices using long-train intra-cortical micro-stimulation (ICMS) has been shown to evoke responses resembling purposeful movements in motor cortices of the macaque monkey. Stimulation of the premotor cortex revealed the presence of 5 movement primitives, including defense, hand-to-mouth, hand in central space, reach-to-grasp, and climbing (Graziano et al., 2005; Graziano, 2006). The reach-to-grasp and hand-to-mouth primitives are of

particular interest with regards to reaching behavior. The reach-to-grasp primitive is evoked from the caudal aspect of dorsal premotor cortex (PMdc). Stimulation of PMdc results in straightening of the wrist, opening of the digits as if to grasp, and reaching of the hand into distal space (Graziano et al., 2005). The hand-to-mouth primitive is evoked from ventral pre-motor cortex (PMv). Stimulation of PMv results in closure of the forefinger against the thumb, supination of the forearm to bring the hand to the mouth, and opening of the mouth (Graziano et al., 2005; Graziano, 2006).

Subcortical areas of the brain involved in reaching behaviour. The cerebellum is located underneath the cerebral cortex, posterior to the pons and medulla. The cerebellum compares the planned movement to the actual movement that is being executed and determines if modifications or error corrections are needed (Mugnaini, 1972; Thach, 1978). As illustrated in Figure 2, the cerebellum contains three distinct lobes that process differential information concerning movement. The spinocerebellum (anterior lobe; medial and intermediate zones) is located adjacent to the midbrain and is concerned with movement execution and muscle tone. The cerebrocerebellum (posterior lobe; lateral zone) lies adjacent to the pons and sends reciprocal connections to the cerebral cortex to aide in planning complex motor actions. The vestibulocerebellum (flocculonodular lobe) is located on the lower part of the cerebellum and is concerned with the control of eye movements, posture, and balance (Middleton & Strick, 1997; Thach, 1972; Thach & Jones, 1979; Brodal, 1978; Schmahmann & Pandya, 1997; Schmahmann, Rosene, & Pandya, 2004).

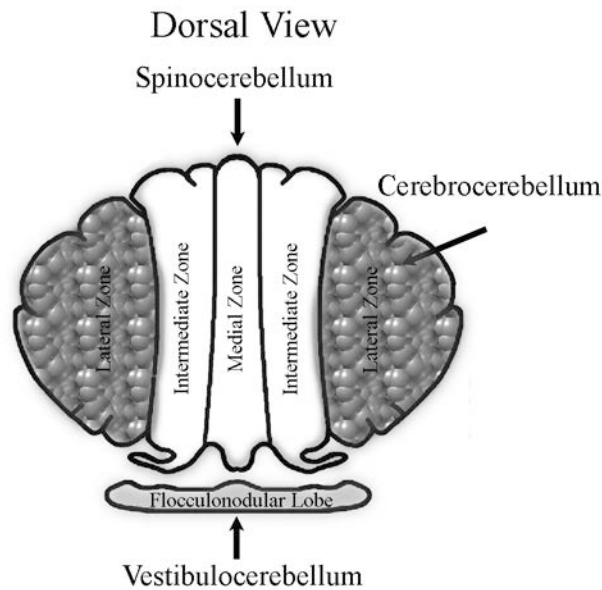


Figure 2. Diagram of the lobes of the cerebellum. The lobes of the cerebellum are shaded in different patterns to illustrate their location and differential role in movement. Adapted from thebrain.mcgill.ca

The cerebellum has two afferent fibres; 1) the climbing fibre – so named because it ascends into the cerebellum and tightly winds along the dendrites of its Purkinje cell, and 2) the mossy fibre – so named for its microscopic appearance (Thatch, 1999). Climbing fibres of the inferior olive of the medulla oblongata collect information from muscle proprioceptors and acts directly excite Purkinje neurons. Mossy fibres of the pontine nuclei collect information from the cerebral cortex and act to indirectly excite Purkinje neurons via the parallel fibres (axons) of granule cells (Ramnani, 2006; Eccles, Ito, & Szentagothai, 1967; Fox & Barnard, 1957; Mink, 1999; Scheiber, 1999). Three other cell types exist within the cerebellum, stellate cells, basket cells, and Golgi cells. Each type is an interneuron, which act to inhibit Purkinje cell activity (Fox & Barnard, 1957; Millers, 2010). The only output pathways of the cerebellum is via the Purkinje cell. All Purkinje cells send inhibitory projections onto neurons of the deep cerebellar nuclei. The intermediate zone of the spinocerebellum projects onto the interpositus nucleus, which projects via the red

nucleus and thalamus (ventrolateral and anterior ventral nucleus) to M1 to make quick, online corrections during movement execution. The cerebrocerebellum projects onto the dentate nucleus, which projects via the thalamus (ventrolateral and anterior ventral nucleus) to premotor areas and M1 to make slower, planned corrections during movement execution (Mugnaini, 1972; Thach, 1978).

The basal ganglia are located at the base of the forebrain and are strongly interconnected with the cerebral cortex and thalamus. The basal ganglia do not influence motor neurons directly, but rather influence movement through their connections with the cerebral cortex, suggesting a modulatory role for basal ganglia in movement production. As illustrated in Figure 3, the basal ganglia are comprised of four principle nuclei: the globus pallidus, the subthalamic nucleus, the substantia nigra, and the striatum. The striatum is itself comprised of two nuclei, the caudate and the putamen, which are separated by the internal capsule (a major collection of fibres that run bi-directionally between the thalamus and neocortex).

The striatum is the major recipient of inputs into the basal ganglia (Mink, 1999). All areas of the cerebral cortex, except for primary auditory and visual cortices, send excitatory (glutamatergic) projections to the medium spiny neurons of the striatum (Cherubini, Herrling, Lanfumey, & Stanzione, 1988; Bouyer, Park, Joh, & Pickel, 1984; Kemp & Powell, 1970; Kemp & Powell, 1971). The striatum sends inhibitory projections to the external segment of the globus pallidus, the internal segment of the globus pallidus, and the substantia nigra pars reticulata. The latter two nuclei give rise to the major output projections of the basal ganglia (Lewis, Caldwell, & Barker, 2003).

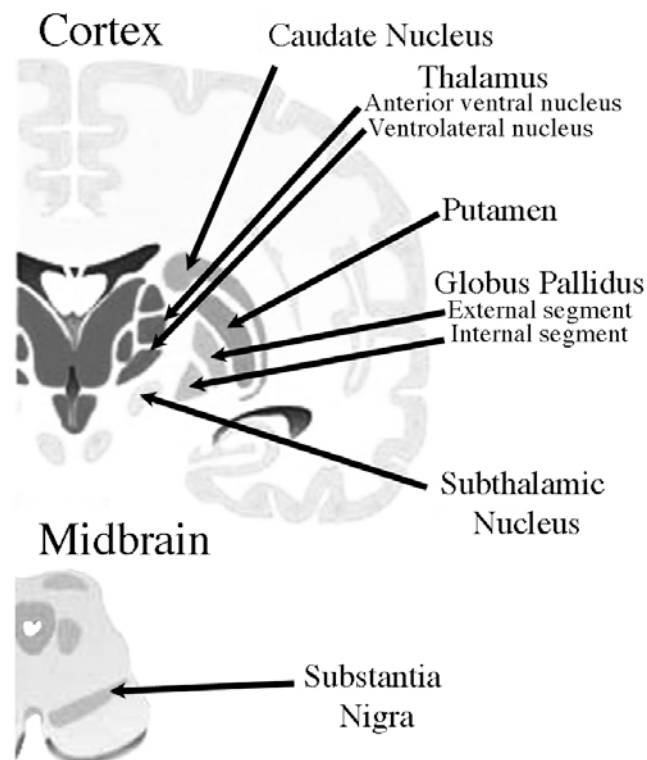
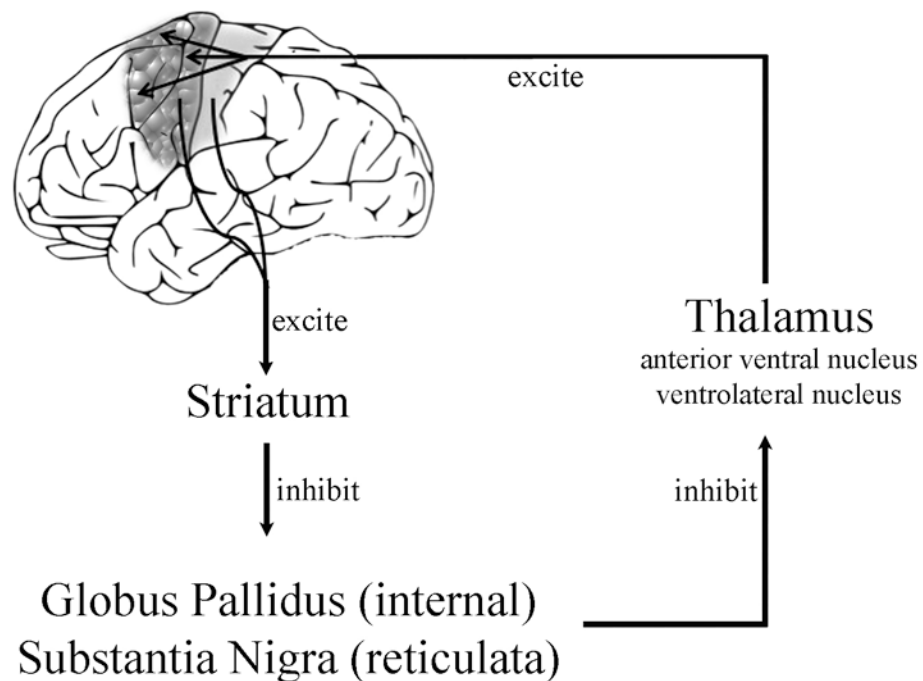


Figure 3. The nuclei of the basal ganglia. The nuclei of the basal ganglia are shaded in different colours. The anterior ventral nucleus and ventrolateral nucleus of the thalamus are also labelled.

The internal segment of the globus pallidus and the substantia nigra pars reticulata work to inhibit their target nuclei in the motor thalamus (ventrolateral and anterior ventral nuclei) and the cerebral cortex, and this tonic inhibition is thought to be modulated by two parallel systems, one direct and one indirect. As illustrated in Figure 4, the direct pathway of the basal ganglia connects the striatum to the internal segment of the globus pallidus and the substantia nigra pars reticulata. Projections from the striatum to the internal segment of the globus pallidus and the substantia nigra pars reticulata are inhibitory, employing GABA and substance P as its neurotransmitters (Penney & Young, 1981; DiFiglia & Rafols, 1988; Francois,

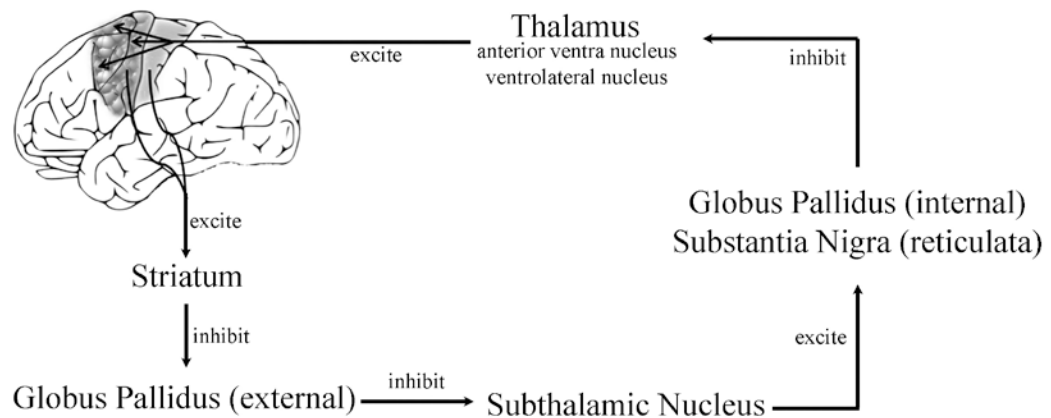
Percheron, Yelnik, & Heyner, 1984; Parent & De Bellefeuille, 1982; Lewis, Caldwell, & Barker, 2003). Axons of the internal segment of the globus pallidus terminate on the ventrolateral nucleus and the ventral anterior nucleus of the thalamus (DeVito & Anderson, 1982). In turn, the thalamic nuclei send excitatory (glutamate) projections to the primary motor, premotor, and supplementary motor cortices, and possibly the prefrontal cortices of the frontal lobe (Middleton & Strick, 1994). Thus, the cortex excites the striatum and the striatum in turn inhibits the internal segment of the globus pallidus. The inhibited internal segment of the globus pallidus then sends less inhibitory signals (disinhibition) to the thalamus, exciting the cortex (Lewis et al., 2003).



Net Effect = Excitation of Motor Cortices

Figure 4. The direct pathway of the basal ganglia. The net effect of the direct pathways is the facilitation of movement.

The indirect pathway of the basal ganglia connects the striatum to the external segment of the globus pallidus (Lewis et al., 2003; Bolam & Smith, 1992). As shown in Figure 5, projections from the striatum to the external segment of the globus pallidus are inhibitory, employing GABA and enkephalin as its neurotransmitters. The external segment of the globus pallidus sends inhibitory (GABA) projections to the subthalamic nucleus (Mink, 1999; Rouzaille-Dubois, Hammond, Hamon, & Fegerm 1980; Kita, Chang, & Kitai, 1983). In turn, the subthalamic nucleus sends excitatory (glutamatergic) projections to the internal segment of the globus pallidus and substantia nigra pars reticulata, the external segment of the globus pallidus, and the substantia nigra pars compacta (Parent, Smith, Filion, & Dumas, 1989; Lewis et al., 2003). The internal segment of the globus pallidus and substantia nigra pars reticulata then send inhibitory (GABA) projections to the anterior ventral and ventrolateral nuclei of the thalamus, which send excitatory (glutamatergic) projections to the cortex. Thus, the cortex excites the striatum and the striatum in turn inhibits the external segment of the globus pallidus. The external segment of the globus pallidus sends less inhibitory signals to the subthalamic nucleus. This frees the subthalamic nucleus to excite the internal segment of the globus pallidus and the substantia nigra pars reticulata, thus inhibiting the thalamic nuclei and the motor cortex (DeVito et al., 1982; Lewis et al., 2003).



Net Effect: Inhibition of Motor Cortices

Figure 5. The indirect pathway of the basal ganglia. The net effect of the indirect pathway is the inhibition of movement

The Corticospinal Tract

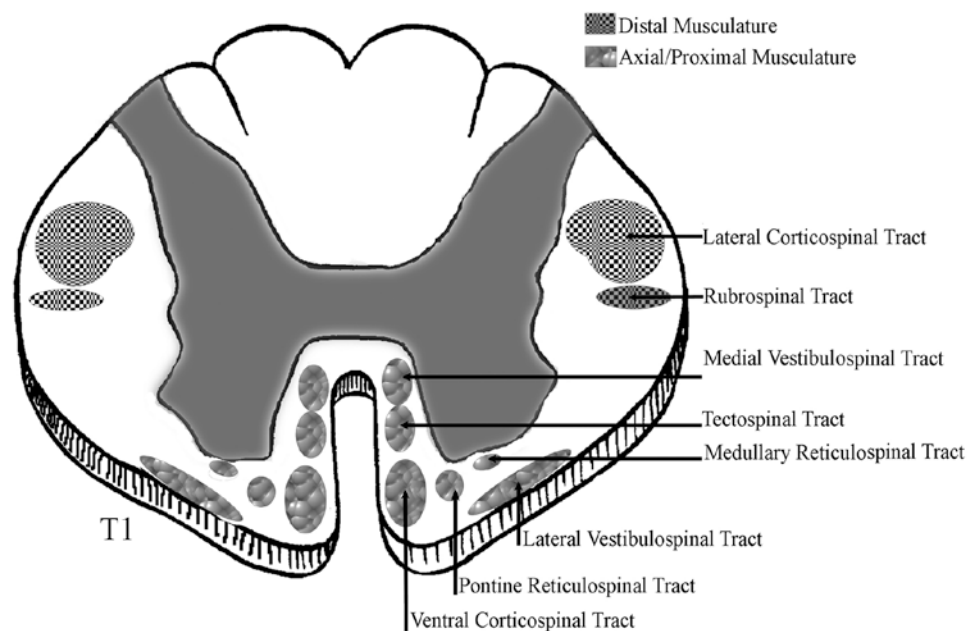
Table 1 briefly describes the descending motor pathways that are mainly involved in reaching behaviour. The major descending motor pathway for reaching behaviour in humans is the corticospinal tract (Schieber, 1999). The corticospinal tract originates from several cortical areas, including M1, dorsal and ventral premotor cortices, supplementary motor cortex (Dum & Strick, 2005; Schieber, 1999), the somatosensory cortex (S1), and the posterior parietal cortex (Lemon, 2008). M1 receives inputs from many areas of the brain, including the prefrontal cortex, S1, the temporal cortex, the parietal cortex, the basal ganglia, and the cerebellum (Ghez & Krakauer, 2000; Pandya & Kuypers, 1969; Jones & Powell, 1970; Johnson, Ferraina, & Caminiti, 1993; Tanne, Boussaoud, Boyer-Zeller, Moret, & Rouiller, 1995; Blatt, Andersen, & Stoner, 1990; Scheiber, 1999; He, Dum, & Strick, 1995; Wise, 1996;

Luppino, Matelli, Camarda, & Rizzolatti, 1993). It is because of the diffuse inputs into M1, as well as the many structures that project into the corticospinal tract, that the corticospinal tract is presumably involved in the control of somatosensation, nociceptive, reflexive, autonomic, and somatic motor functions in addition to voluntary motor behaviour (Lemon, 2008).

Corticospinal neurons have large pyramidal-shaped somata in layer V of the cortex. The axons of corticospinal neurons of the upper and lower limbs and trunk leave the cortex and traverse the posterior limb of the internal capsule. The internal capsule is a bundle of myelinated fibres that divide the striatum into the caudate and putamen (Lemon, 2008). As the axons leave the internal capsule, they course through the cerebral peduncles (midbrain), and through the motor nuclei of the pons. At the junction of the medulla and the spinal cord, the fibres form the medullary pyramid, where the majority of corticospinal axons cross the midline to form the lateral corticospinal tract (pyramidal decussation). A minority of corticospinal axons remain on the same side and form the ventral corticospinal tract (Lemon, 2008; Thatch, 1999). The lateral corticospinal tract synapses directly onto motor neurons in laminae IX in the lateral part of the ventral horn or to interneurons in the intermediate zone, and controls the distal musculature of the arms and legs on the contralateral side of the body. The ventral corticospinal tract synapses onto motor neurons in laminae VII and VIII in the ventromedial horn and controls the proximal musculature of the trunk on the ipsilateral side of the body (Thatch, 1999; Schieber, 1999).

Table 1. Descending Pathways of the Brain involved in Reaching Behaviour

Descending Pathway	Origin	Role(s)
Ventromedial Brainstem Pathways		
Interstitiospinal Tract	Tagmentum	Control of axial and proximal musculature
Tectospinal Tract	Superior Colliculus	Head/neck reflex to stimuli
Vestibulospinal Tract	Vestibular Nuclei	Head/neck reflex to stimuli
Pontine Reticulospinal Tract	Pons	Keep head balanced
Medullary Reticulospinal Tract	Inferior Olive	Enhances anti-gravity reflexes of spinal cord
		Inhibits anti-gravity reflexes of spinal cord
Dorsolateral Brainstem Pathways		
Rubrospinal Tract	Red Nucleus	Control of distal musculature
		Distal musculature, especially hands
Ventral Corticospinal Tract	Motor Cortices	Proximal musculature of the trunk
Lateral Corticospinal Tract	Motor Cortices	Distal musculature of that arms and feet



Not all of the projections from cortical motor areas terminate within the spinal cord. Many of the axons from layer V of motor cortex project to the basal ganglia and cerebellum, two major subcortical structures involved in motor behaviour (Schieber, 1999; Ghez et al., 2000). Thus, the basal ganglia and the cerebellum can be viewed as funnels that gather information from the cerebral cortex and then send this processed information back to cortical motor areas to modulate motor output.

Visual Control of Reaching

An important component of reaching behaviour is the visual control of the arm and hand. Before the hand can reach towards an object and pre-shape the digits to grasp the object, the eyes first fixate the object to garner its intrinsic and extrinsic properties (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008; Milner & Goodale, 2008). Movement of the eye in its orbit is carried out by six muscles; the inferior rectus rotates the eye downward and towards the midline, the superior rectus rotates the eye upward and towards the midline, the inferior oblique rotates the eye upward and away from the midline, the superior oblique rotates the eye downward and away from the midline, the medial rectus rotates the eye towards the midline, and the lateral rectus rotates the eye away from the midline (Goldberg, 2000).

A network of cortical and subcortical nuclei controls voluntary saccade production in humans, as illustrated in Figure 6. The superior colliculus is the major visuomotor region of the mammalian brain, in which cortical and subcortical inputs converge and are integrated (Munoz & Everling, 2004). The intermediate and deep layers of the superior colliculus receive inputs from supplementary eye fields, frontal eye fields, dorsolateral prefrontal cortex, and the substantia nigra pars reticulata (Glimcher, 1999; Goldberg, 2000). Supplementary eye fields are involved in the sequencing of saccades (Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000; Martinez-Trujillo, Medendorp, Wang, & Crawford, 2004), the dorsolateral prefrontal cortex suppresses automatic/reflexive responses (Munoz & Everling, 2004), and the substantia nigra pars reticulata assists in the maintenance of visual fixation (Mink, 1999; von Krosigk, Smith, Bolam, & Smith, 1992; Hikosaka, Takikawa, & Kawagoe,

2000; Parent & Hazrati, 1995; Smith, Bevan, Shink, & Bolam, 1998). Frontal eye fields play a crucial role in voluntary saccade production. Movement-related neurons of the frontal eye fields send excitatory projections to the 1) movement-related neurons in the intermediate layers of the superior colliculus to initiate movement commands and 2) basal ganglia to inhibit the substantia nigra pars reticulata (to release visual fixation) (Jiang, Stein, & McHaffie, 2003; Cebrian, Parent, & Prensa, 2005; Hikosaka & Wurtz, 1983; 1985; Carpenter, Nakano, & Kim, 1976; Mink, 1999; Hanes & Wurtz, 2001). The superior colliculus and the frontal eye fields send projections to the paramedian pontine reticular formation to initiate the desired saccade (Schiller, True, & Conway, 1980; Munoz et al., 2004).

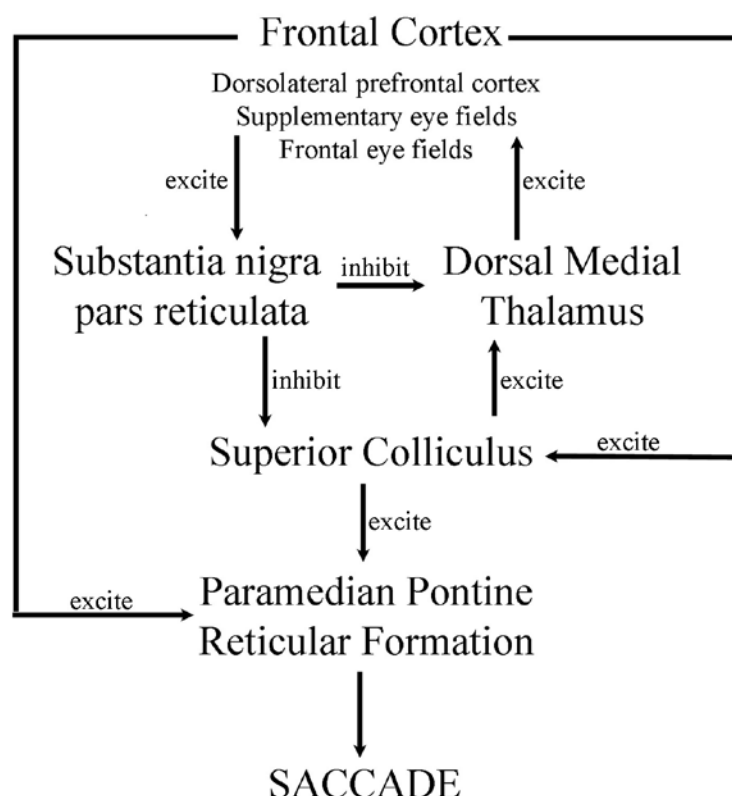


Figure 6. Diagram of the voluntary saccade system in humans (Adapted from Munoz & Everling, 2004).

Development of the Corticospinal Tract for Skilled Forelimb Movement

Use of the arm and hand to perform purposeful reaching movements is a learned behaviour that develops gradually and reflects the maturational state of the brain (Kuypers, 1981; Armand, Olivier, Edgley, & Lemon, 1997; Olivier, Edgley, Armand, & Lemon, 1997; White, Castle, & Held 1964; Wallace & Whishaw, 2003). Neural systems controlling proximal musculature and the trunk and shoulders mature first, followed by distal musculature of the limbs and hands (Berthier, Clifton, McCall, & Robin 1999; Kuypers, 1962; Lawrence & Hopkins, 1976; Porter & Lemon, 1993; Wallace & Whishaw, 2003). Control of the hand is dependent on direct connections from pyramidal neurons in motor cortex to alpha motor neurons of the spinal cord. These connections are established between seven and twelve months postnatal age, at the approximate time when visually guided movements of the hand become refined (Butterworth, Verweij, & Hopkins, 1997; Halverson, 1931; Halverson, 1937).

In addition to establishing neuronal connections between the brain and spinal cord, functionality of the motor tract is dependent upon fibre tract myelination. Myelination of the corticospinal tract begins during the third trimester (Eyre, Miller, Clowry, Conway, & Watts, 2000; Brody, Kinney, Kloman, & Gilles, 1987; Wozniak & O'Rahilly, 1982; Yakovlev & Lecours, 1967). Premature infants born between 30 and 36 weeks gestational age show myelination of the medulla, dorsal pons, the inferior cerebellar peduncles, and the posterior internal capsule (McArdle, Richardson, Nicholas, Mifakhraee, Hayden, & Amparo, 1987), with full-term newborns showing additional myelination in the ventral pons and superior peduncles

(Ballesterous, Hansen, Soila, 1993). The internal capsule is fully myelinated by 5 months of age, and myelination expands into the four lobes of the brain by the end of the first year (Ballesterous et al., 1993). By two years of age, the appearance of the brain is almost identical to that of the adult human, with myelination of subcortical association fibers continuing into early adulthood (Ballesterous et al., 1993). These findings are summarized in Figure 7.

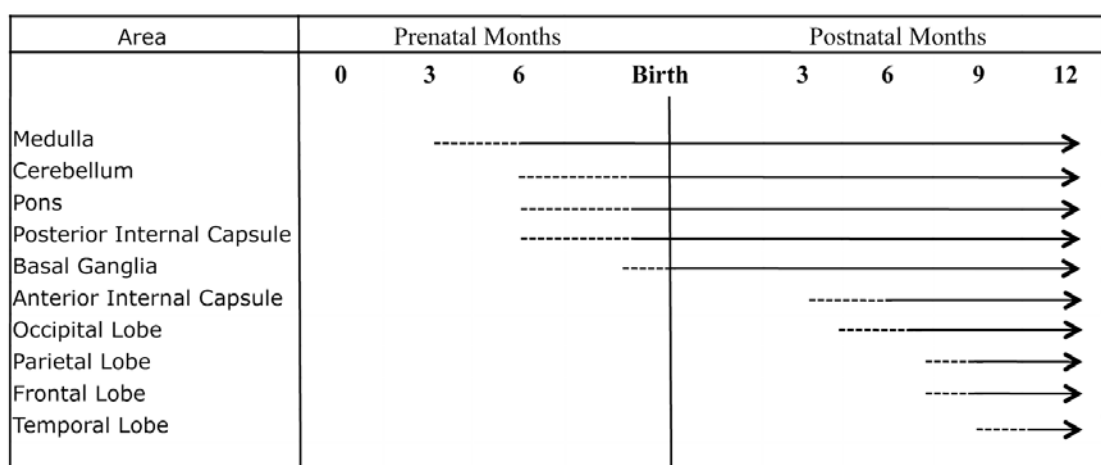


Figure 7. Diagram of myelination progression during prenatal and postnatal development. The dashed portion of the line indicates the approximate onset of myelination and the solid line indicates the presence of myelination. (Adapted from Valk & van den Knaap, 1989).

Diseases of the Motor System

The 19th century neurologist John Hughlings Jackson was the first to recognize that lesions of the nervous system could result in two different syndromes. Negative signs reflect the loss of normal capacities, for example, the loss of muscle tone, whereas positive signs reflect the gain of abnormal capacities, for example,

jerkings of the extremities (Ghez & Krakauer, 2000). Although there is a variety of movement impairments that can result from lesions throughout the brain, the two most studied “motor disorders” are Parkinson’s disease (PD) and Huntington’s disease (HD).

Parkinson’s disease. Parkinson’s disease was first described by James Parkinson in 1817 (Parkinson, 2002) and is characterized by impaired movement initiation, a progressive reduction in amplitude and velocity of voluntary movements, muscular rigidity, and a resting tremor. Other symptoms include impairments to voluntary movements, shuffling gait, stooped posture, masked face, and impaired balance (Halliday, Lees, & Stern, 2011).

Parkinson’s disease was the first brain disorder identified as caused by the deficiency of a single neurotransmitter. In the mid-1950s, Carlson showed that the Parkinsonian brain had an 80% reduction of dopamine in the basal ganglia, and in the 1960s, it was discovered that the source of the dopamine reduction was the loss of the dopamine producing cells of the substantia nigra pars compacta (Dauer & Przedborski, 2003; Dickson, Braak, Duda, et al., 2009). The substantia nigra pars compacta is a nucleus of the midbrain and is so named for its dark pigmentation (‘substantia nigra’ is Latin for ‘black substance’; Hedreen & De Long, 1991).

The substantia nigra pars compacta projects to all areas of the striatum, modulating excitatory projections from the cortex (Mink, 1999; Hedreen & De Long, 1991). As shown in Figure 8, the loss of dopamine from the substantia nigra affects

both the direct and indirect pathways of the basal ganglia (Penney & Young, 1986; Albin, Young, & Penney, 1989).

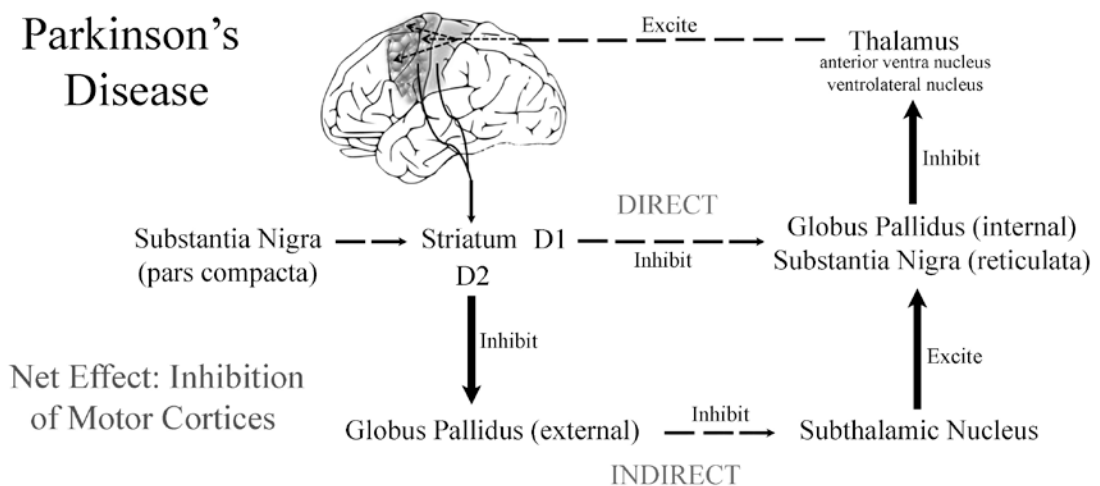


Figure 8. The direct and indirect pathways of the basal ganglia of the Parkinsonian brain. The net effect of the loss of dopamine is inhibition of the motor cortices.

There are two dopamine receptors that play key roles in the basal ganglia. Dopamine has an excitatory effect on the D1 receptors of the direct pathway. Thus, a diminished substantia nigra pars compacta results in the loss of dopamine (and excitatory input) into the striatum. This, in turn, disinhibits the internal segment of the globus pallidus and the substantia nigra pars reticulata, with the net effect of inhibiting the thalamocortical pathway. Dopamine has an inhibitory effect on the D2 receptors of the indirect pathway. Thus, a diminished substantia nigra pars compacta results in a loss of dopamine (and inhibitory input) into the striatum. This, in turn, inhibits the external segment of the globus pallidus and disinhibits the subthalamic nucleus. The subthalamic nucleus then sends increased excitatory projections to the

internal segment of the globus pallidus and the substantia nigra pars reticulata, with the net effect of inhibiting the thalamocortical pathway. The overall result of the disruption of the direct and indirect pathways is the hypokinesia characteristic of PD.

Huntington's disease. Huntington's disease is characterized by involuntary movements, such as slow, writhing movements of the extremities and random movements of the limbs and face (Walker, 2007; Ross, Margolis, Rosenblatt, Ranen, Becher, & Aylward, 1997). Other symptoms include impairment to voluntary movements and the later development of bradykinesia and rigidity (Nance, 1998; Quinn & Schrag, 1998; Thompson et al., 1988).

Huntington's disease was described as an inherited disorder following George Huntington's familial descriptions in 1872 (Huntington, 1872). Huntington's disease was the first complex human disorder identified as caused by a single gene. In 1983, the location of Huntington's disease was mapped onto chromosome 4, and in 1993, the gene associated with Huntington's disease was identified as the HTT gene (Huntington's Disease Collaborative Research Group, 1993). The first exon of the HTT gene contains repeats of the trinucleotide sequence 'CAG', which codes for the amino acid glutamine. A normal copy of the gene contains less than 35 repeats and the Huntington copy of the gene contains more than 40 repeats (Zuccato, Valenza, & Cattaneo, 2010; Langbehn, Brinkman, Falush, Paulsen & Hayden, 2004).

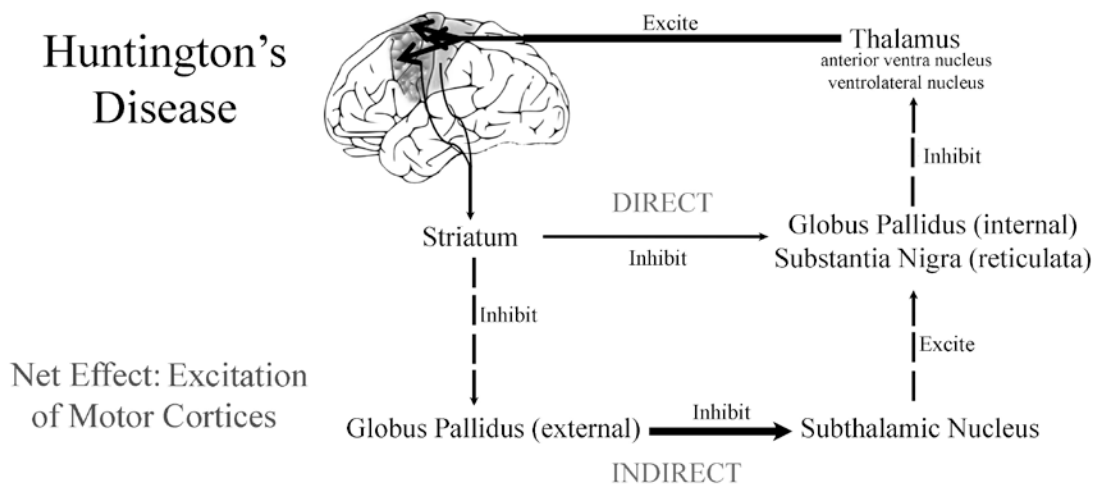


Figure 9. The direct and indirect pathways of the basal ganglia of the Huntington brain. The net effect of the degenerated caudate is excitation of motor cortices.

Pathological studies suggest that the medium spiny neurons of the caudate that give rise to the indirect pathway (project to the external segment of the globus pallidus) are preferentially affected (Vonsattel, Myers, Stevens, Ferrante, Bird, & Richardson, 1985; Kowall, Ferrante, Beal, et al., 1997). As illustrated in Figure 9, the diminished inhibitory input from the caudate disinhibits the external segment of the globus pallidus. In turn, the external segment of the globus pallidus inhibits the subthalamic nucleus and thus inhibits the internal segment of the globus pallidus and the substantia nigra pars reticulata (Crossman, 1987; Albin et al., 1989; Gertler, Chan, & Surmeier, 2008; Surmeier, Ding, Day, Wang, & Shen, 2007). The inhibited internal segment of the globus pallidus and the substantia nigra pars reticulata disinhibits the thalamocortical pathway, resulting in the hyperkinesia characteristic of HD (Albin et al., 1990; Sapp et al., 1995).

As the disease progresses, the medium spiny neurons of the direct pathway become affected and Parkinsonian-like symptoms emerge (Albin et al., 1990). At later stages of the disease, the whole brain appears atrophied, with neuropathological changes in the cerebral cortex, globus pallidus, subthalamic nucleus, substantia nigra, thalamus, hypothalamus, and cerebellum (Thu et al., 2010; Heinsen et al., 1996; Rosas et al., 2003; Vonsattel & diFiglia, 1998).

Sensorimotor Integration

Sensorimotor integration is the process by which sensory input from the body or the environment guides motor output. Such sensory information can include visual, auditory, tactile, olfaction, and proprioceptive stimuli, amongst others. With respect to reaching-to-eat behaviour, a network of sensory and motor nuclei works together to transform sensory information regarding a target food item, into the appropriate motor output to grasp and eat the target. As shown in Figure 10, these areas include the occipital, parietal, and frontal cortices.

The movement primitives that comprise reach-to-eat behaviour include advancing a hand towards a target to grasp (hereafter “*advance*”) and withdrawing the grasped target to the mouth for eating (hereafter “*withdrawal*”; de Bruin et al., 2008). Long-train intracortical microstimulation of premotor and motor cortices of macaque monkeys revealed the differential locations of the movement primitives of advance and withdrawal (Graziano, 2006; Graziano et al., 2005). Advancement of the hand to grasp a target is elicited from dorsal premotor cortex, whereas withdrawing the hand to place the target in the mouth is elicited from ventral premotor cortex. More

to-eat behaviour. That is, the parietal reach region projected onto dorsal premotor cortex and both the ventral and anterior intraparietal regions projected onto ventral premotor cortex (Kaas et al., 2011).

The reach-to-eat regions of the parietal lobe receive direct or indirect inputs from both visual and somatosensory cortices to help guide the movement (Stepniewska, Cerkevich, Fang, & Kaas, 2009). The parietal reach region ('Reach' in Figure 10) and anterior intraparietal region ('Grasp' in Figure 10) receive both visual and somatosensory inputs, whereas the ventral intraparietal region ('Hand to Mouth' in Figure 10) receives only somatosensory inputs. This is interesting with respect to reach-to-eat behaviour, in that it suggests that the 'Reach' and 'Grasp' components are supported by both visual and somatosensory feedback, whereas the 'Hand to Mouth' component is supported solely by somatosensory feedback. An understanding of how the different sensory systems interact with the motor regions of both the parietal and frontal lobes to control reach-to-eat behaviour was the purpose of the present thesis.

Rationale for Thesis

The purpose of the present thesis was to determine the role of sensory attention in reach-to-eat behaviour. Sensory attention is a cognitive process in which an individual guides his or her movements using sensory feedback from the target and/or body. For example, visual attention is used to determine intrinsic

characteristics of the target, whereas somatosensory attention is used to determine the distance of the fingertips to the mouth (de Bruin et al., 2008).

The experiments in this thesis were designed with two purposes in mind: 1) to characterize the motor and sensory development of the reach-to-eat movement in healthy developing infants, and 2) to characterize changes to the movement and sensory control of the reach-to-eat movement in pathological disease of the motor system. Four experiments were conducted and form the major part of the thesis.

Theory

Reaching-to-eat is comprised of two separate movements, each of which has its own target and sensory control.

Hypotheses

1: There is a shared control by vision and somatosensation.

Vision guides hand advance and grasping, whereas somatosensation guides hand withdrawal and placement into the mouth.

2: Sensory control is integrated during development

Infants will show a reliance on visual attention early on in the development of the reach-to-eat movement

3: Brain disorders differentially affect sensory control

Subjects with basal ganglia diseases will show a reliance on visual attention to complete the reach-to-eat movement.

Experiments

The hypotheses were tested in four experiments.

Experiment 1. *Development of Rotational Movements, Hand Shaping, and Accuracy in Advance and Withdrawal for the Reach-to-Eat Movement in Human Infants Aged 6 to 12 Months.* This experiment was designed to examine the developmental profile of the reach-to-eat movement in healthy infants aged six to twelve months. The movement components of the reaching act were evaluated at six, seven, eight, nine, ten, eleven, and twelve months of age. The results suggests that infants (1) gradually develop mature rotational movements of the hand and hand shaping movements, (2) integrate the movements of the hand with trunk, head, and arm movement, and (3) become increasingly smooth and accurate in targeting objects and the mouth, and increasingly use a preferred hand.

Experiment 2. *Development of Visual and Somatosensory Attention for the Reach-to-Eat Movement in Human Infants Aged 6 to 12 Months.* This experiment was designed to examine the development of sensory attention of the reach-to-eat movement in healthy infants aged six to twelve months. The visual attention of the arm, as well as targeting accuracy, were evaluated at six, seven, eight, nine, ten, eleven, and twelve months of age. The results suggest that (1) vision becomes coupled

to hand advance and somatosensation becomes coupled to hand withdrawal, (2) shaping of the hand changes from a whole hand grasp to a pincer grasp to purchase the target item, and (3) the accuracy in grasping the target and in bringing the target to the mouth improved with age.

Experiment 3. *Drug Treatment and Familiar Music Aids an Attention Shift from Vision to Somatosensation in Parkinson's Disease on the Reach-to-Eat Task.*

This experiment was designed to examine the changes to the reach-to-eat movement in the motor disorder Parkinson's disease, and the effect of drug and music treatment on motor performance. The results suggest that 1) individuals with Parkinson's disease are impaired on the movement components and visual attention of the reach-to-eat movement; 2) drug treatment and music therapy ameliorate the impairments in visual attention; and 3) drug treatment and music therapy do not affect impairment to the motor component.

Experiment 4. *Proximal Movements Compensate for Distal Movement Impairments in a Reach-to-Eat Task in Huntington's Disease: New Insights into Motor Impairments in a Real-World Skill.* This experiment was designed to examine the changes to the reach-to-eat movement in the motor disorder Huntington's disease. The results suggest that 1) individuals with Huntington's disease are impaired on the movement components and visual attention of the reach-to-eat movement; 2) proximal parts of the arm and trunk compensate for impairments in the distal arm during the reaching act; and 3) individuals with Huntington's disease show an impairment in the timing and termination of motion.

Behavioural Task and Assessment

Several measures were used to examine the development and/or disturbances to the reach-to-eat movement. Not every measure was used in each experiment but a description of all the measures are summarized in the following section.

Reaching Task

Infants. *Six- to nine-months-old:* Infants are seated in a neck and back supportive chair, with the hands and arms free to grasp and manipulate objects, see Figure 10A. The parent holds a target toy at an approximate distance of the infants arm's length at the midline of the infants body. The infant reaches towards the toy, grasps the toy with the hand(s), and withdraws the toy to the mouth for oral exploration. The trial ends when the toy was placed into the mouth. Once the target was taken from the mouth, the parent removed the toy and a new toy was offered to initiate a new trial.

Nine and a half- to twelve-months-old: Infants are seated in a high chair with the tray table attached, with the hands and arms free to grasp and manipulate objects, see Figure 10B. The parent places a small food item (e.g., Cheerios™) or small toy on the high chair tray. The infant reaches towards the food item/small toy, grasps it with the hand, and withdraws it to the mouth for eating/oral exploration. The trial ends when the food item is released into the mouth and the hand is carried away from the mouth and held in a resting position or the small toy is brought to the mouth for oral

exploration. The parent then either places a new food item on the tray to initiate a new trial or removes the toy from the mouth and places a new toy on the tray.

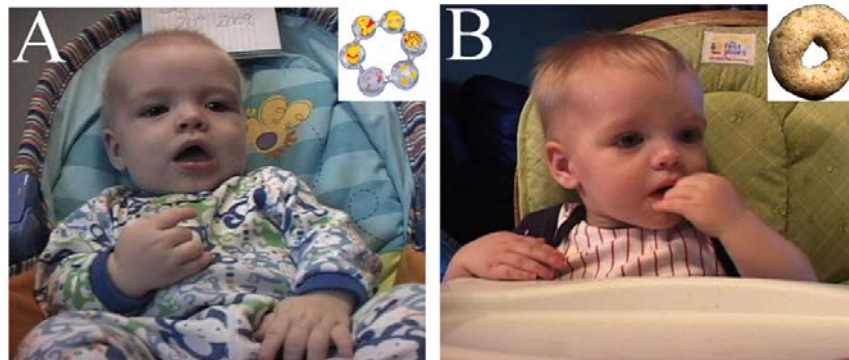


Figure 11. A) Six- to nine-month-old infants reach for small toys (inset) presented at the midline of the body. B) Nine and a half- to twelve-month-old infants reach for small food items (inset) or small toys placed on the tray.

Adults. Subjects perform a seated reach-to-eat task in which they reach toward a pedestal for a small food item that is grasped and withdrawn to the mouth for eating (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008; Whishaw et al., 2002). Subjects are seated in a comfortable upright position, with their feet flat on the floor (Figure 11). A self-standing height adjustable pedestal is placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° extension) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion).

Once subjects are seated, they are asked to place their hands palm down on their thighs, and this instruction is not repeated. The experimenter stands to the left of the subject (i.e. in peripheral visual space) and places a food item (Cheerio™) on the pedestal for each trial. The subjects are instructed to reach for food with their

dominant hand. Each testing trial is initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure. Each trial concludes following successful placement of the food item in the mouth and the return of the reaching hand to its start position on the lap. The experimenter maintains a casual relationship with the subject, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition. Because subjects are not informed that their eye movements are under investigation, they are not asked to fixate on an object in the environment prior to trial initiation.

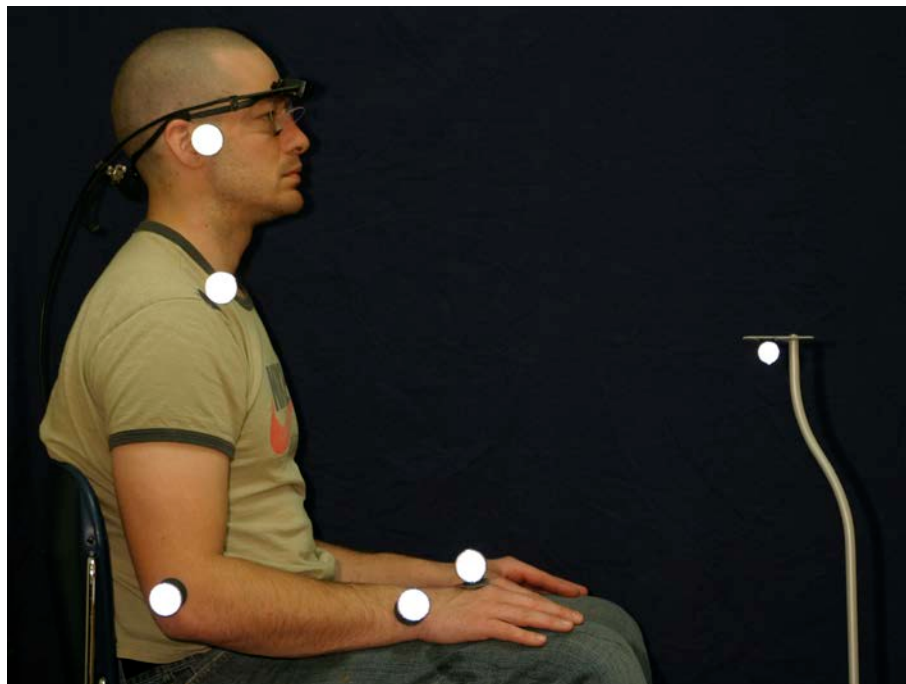


Figure 12. A subject sits before a pedestal on which a food item is placed with the hand open flat on the lap. The white dots represent the light reflective markers on the subject (left) and the pedestal (right). The subject is wearing eye-tracking glasses (head) to monitor visual attention of the reaching movement.

Behavioural Assessment

Reach duration. A digital video camera is positioned sagittal to the subject to record a reach-side view of the subject from lower leg to head at a sampling frequency of 30 Hz. Trial reaches are digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the ulnar styloid process (reach wrist). The data are acquired via a manual mode, digitizing the moving points by cursor. The ulnar styloid process is analyzed to determine movement duration and velocity during the different phases of the reach-to-eat movement (de Bruin et al., 2008).

The events of movement onset and offset are determined from the resultant reach wrist velocity using a custom-written algorithm (Microsoft Excel 2002), with minimal resultant velocity used to indicate the onset and offset events for the movement phases of the reach-to-eat movement. The reach-to-grasp phase is defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the food item). The grasp-to-eat phase is defined as the time between the second velocity onset (i.e. first movement of hand away from pedestal) and the subsequent point of minimal velocity (i.e. as the food item contacts the mouth). *The total reach duration* is defined as the time between initial velocity onset (i.e. first movement of the hand) and the second subsequent point of minimal velocity (i.e. as the food item contacts the mouth).

Visual attention. Subjects wear a head-mounted infrared eye tracking system

(subject is wearing them in Figure 10; MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) to track eye movements with a sampling frequency of 30 Hz (de Bruin et al. 2008). The video record of the data collected by the eye tracking system are subjected to off-line analysis to determine the following events of visual attention: engage-to-move, grasp-to-disengage, and total engagement period. *Engage-to-move* is defined as the time between the first point that the eyes descend to visually fixate the food item and first movement of the forelimb towards the food item, and *grasp-to-disengage* is defined as the time between contact of the food item with the digits and the first point that the eyes disengage from the food item. *The total visual engagement period* is defined as the time between the first point that the eyes descend to fixate the food item (*engage*) and the first point that the eyes ascend (*disengage*) from the food item. A visual marker presented at the onset of the testing session is used to time-synchronize the video record of the reach wrist obtained from the digital camera and the video record from the eye-tracking system offline using Final Cut Pro HD v.4.5 for Mac OS X v.10.2.8.

Skilled reaching rating scale. The reach-to-eat movement is measured using a modified version of the movement element rating scale (Whishaw et al., 2002). As is described in Table 2, the following measures are assessed: (1) Orient – head and eyes orient to the target prior to arm and hand movement; (2) Lift – supination of the hand following lift from the lap; (3) Advance – the forelimb moves towards the target; (4) Pronation - pronation of the hand over the food item; (5) Grasp – arm remains still as digits close around the food item; (6) Supination – hand rotates immediately following grasp and again as hand/food nears the mouth; (7) Release – food is placed in the mouth.

A score of 0 is given if the movement is present and normal, 0.5 if the movement is present but abnormal, and a score of 1 is given if the movement is absent.

Table 2. Skilled Reaching Rating Scale

Component	Element	Sub-Element	Description
Orient	Orient	A	Head is moving freely then fixes on target at beginning of trial
		B	Eyes fixate target prior to movement of hand/reach
Transport	Lift	A	Initial hand lift due to flexion of the elbow
		B	Digits semi-flex
		C	Hand supinated approximately 30 degrees
		D	Tips of digits are brought towards the midline of the body
	Advance	A	Hand takes shortest path to target
		B	Hand stops directly above the target
		C	Trunk leans to the side opposite reach
	Pronation	A	Digits open and extend over the food target
		B	Knuckle on reaching hand forms horizontal line
		C	Elbow opens to full arm length as subject reaches
Grasp	Grasp	A	Thumb and index finger grasp food item
		B	Digits 3-5 remain still as grasp is executed
		C	Wrist extends to lift food item from platform
Withdrawal	Supination	A	Reaching hand supinates 45 degrees immediately after vertical lift
		B	Hand supinates another 45 degrees when in close proximity to the mouth
Release	Release	A	Finger tips contact lips for placement of food item in mouth
		B	Digits open to release food item into mouth
		C	Hand is placed on lap with fingers extended and palm down
		D	Trunk leans back towards midline
Disengage	Disengage	A	Eyes look away from target at tactile contact

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Chapter 2

**Development of rotational movements, hand shaping, and accuracy in advance
and withdrawal for the reach-to-eat movement in human infants aged 6 to 12
months**

Abstract

The reach-to-eat movement, transport of a hand to grasp an object that is withdrawn and placed in the mouth, is amongst the earliest developing functional movements of human infants. The present longitudinal study is the first description of the maturation of hand-rotation, hand shaping, and accuracy associated with the advance and withdrawal phases of the movement. Eight infants, aged six months to twelve months, and eight adults, were video recorded as they reached for familiar objects or food items. Hand, arm, and trunk movements were assessed frame-by-frame with the Skilled Reaching Rating Scale, previously developed for the assessment of adult reaching, and supplementary kinematic analysis. Reach-to-eat maturation was characterized by three changes. First, for advance, a simple open hand transport gradually matured to a movement associated with pronation and hand shaping of the digits for precision grasping. Second, for withdrawal to the mouth, a direct withdrawal movement gradually became associated with hand supination that oriented the target object to the mouth. Third, associated with the maturation of rotational movements, inaccurate and fragmented hand transport and withdrawal movements developed into precise targeting of the hand-to-object and object-to-mouth. Across the age range, there was a decrease in bimanual reaching and an increase in right handed reaching. The results are discussed in relation to the idea that the maturation of the reach-to-eat movement involves the development of rotational and shaping movements of the hand and visual and somatosensory guidance of a preferred hand.

Bringing the hand and objects to the mouth is such a pronounced behavior in human infants (Piaget, 1952; Lew & Butterworth, 1997; Rochat, 1989) that Butterworth and Hopkins (1988) have postulated that it is supported by an orally-elicited neural system. Foetuses will bring a hand to the face and place the thumb in the mouth (Myowa-Yamakoshi & Takeshita, 2006; De Vries, Wimmers, Ververs, Hopkins, Savelsbergh, & van Geiln, 2001; De Vries, Visser, & Prechtl, 1982). Newborn infants hold their hands by their face (Sacrey & Whishaw, 2010), bring a hand to the mouth to self-sooth (Hopkins, Janssen, Kardaun, & van der Schoot, 1988; Feldman & Brody, 1978), and hold the breast and a bottle to nurse (Widstrom, Lilja, Aaltomaa-Michalias, Dahllof, Lintula, & Nissen, 2011). Three-month-old infants clasp their hands at the midline in an attempt to reach a visual target (Atkinson, 1984; Bruner & Koslowski, 1972; Hopkins & Prechtl, 1984; Von Hofsten, 1991) and open their mouth in preparation to grasp at the same time (Butterworth et al., 1988; Bruner et al., 1972; Foroud, 2008). At four months of age, objects are grasped and brought to the mouth with bimanual movement (von Hofsten & Lindhagen, 1979). At 6 months of age, objects are grasped and brought to the mouth with unimanual movements (von Hofsten, 1991). By 10 months of age, precision grips are developed (Napier, 1956; Connolly & Elliott 1972). These oral-manual movements of infants are a precursor to the everyday activity of reaching-to-eat in adults (de Bruin, Sacrey, Doan, Brown, & Whishaw, 2008; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Sacrey, Clark, & Whishaw, 2009).

Although the overt act of reach-to-eat has been documented in infants (Napier, 1956; Desmurget, Prablanc, Arzi, Rossetti, Paulignan, & Urquizar, 1996; Fan, He, &

Helms Tillery, 2006), the accuracy and component movements of the limb and hand (Jeannerod, 1984, 1988, 1999) have not been fully described. Such a description is important for a number of reasons. First, documentation would provide further milestones for an every-day occurring behavior of infants (Piaget, 1952). Second, insights into the development of the movement might prove useful in diagnosing and documenting developmental disorders (Coluccini, 2007). Third, a description of the development of reaching-to-eat behaviour would be useful in documenting the parallel development of sensory-neural processes supporting hand use (de Bruin et al, 2008; Corbetta et al, 2009). Such a description would also be relevant to theoretical formulations suggesting that there are different forms of adult reaching, e.g., online reaching mediated by the dorsal cortical stream versus conscious reaching mediated by the ventral cortical stream (Goodale & Milner, 1992). Thus, in the present study, infant reach-to-eat movements were analysed for component elements using the Skilled Reaching Rating Scale (SRRS), previously developed for the assessment of adult reaching, and kinematic analysis of movement trajectory (Foroud & Whishaw, 2012; Whishaw et al., 2002).

Healthy infants were filmed monthly from six to twelve months of age as they reached for familiar objects or food items that they brought to the mouth. Six- to nine-month-old infants reached for familiar small toys and ten- to twelve-month-old infants reached for familiar small food items or small toys. Adults reached for similar items. Reaches were analyzed frame-by-frame and components of reaching were scored using the Skilled Reaching Rating Scale. Hand trajectory and hand rotation were measured using a digitizing program and accuracy was scored for both advance and withdrawal movements.

Materials and Methods

Subjects

Healthy infants. Nine healthy, full term infants (five boys and four girls) participated in the study. Consistent with the average population of southern Alberta, all infants were Caucasian. The infants were born with uncomplicated deliveries and were healthy, with no known sensory, motor, or neurological impairment. The infants were recruited from acquaintances of an author (LRS). At the beginning of the study, infants were six months of age ($M \pm SD = 6 \text{ months } 0.5 \pm 0.76 \text{ days}$) and at the end of the study, infants were twelve months of age ($M \pm SD = 12 \text{ months } 1.63 \pm 2.26 \text{ days}$). One baby (a male) was excluded from analysis due to incomplete video-recording procedures. Informed consent was obtained from the parent(s) prior to the onset of the study and parents agreed to follow a prepared video recording protocol. At the end of the study, the parents were given the Sony miniDV video camera with which they filmed their children, to thank them for participating in the study.

Healthy adults. Eight healthy young adults ($M \pm SD = 18.90 \pm 0.99 \text{ years}$) also participated in the study to determine the adult norm for the reach-to-eat movement. Consistent with the average population of southern Alberta, all adults were Caucasian. The adults were self-reported to be in good health with no history of neurological disorder, were right handed, and all had normal or corrected to normal vision. The adults were recruited from an undergraduate class at the University of Lethbridge and received course credit for their participation. Informed consent was

obtained from subjects prior to the initiation of the testing session. The University of Lethbridge Human Subjects Research Committee approved the study.

Procedure

Infants and adults performed a seated reach-to-eat task in which they reached towards a target that was grasped by the hand and withdrawn to the mouth (Whishaw et al., 2002; Melvin et al., 2005; de Bruin et al., 2008). Infants were video-recorded at their place of residence by their parents (Sacrey & Whishaw, 2012), monthly, from six months of age to twelve months of age. Video recording began as infants turned six months of age because goal directed reaching becomes reliable after six months of age (Bower, 1974; Bruner, 1969) and continued until the infants turned 12 months of age, an age at which infants develop precision grasping (von Hofsten & Fazel-Zandy, 1984).

To avoid a potential choking hazard, six- to nine-month-old infants reached for small toys and ten- to twelve-month-old infants reached for small food items to eat. If the older infant was not interested in reaching for food items, a small toy was placed on the tray to elicit reaching movements (see below). Analysis revealed infants used the same movements when reaching for small food items and small toys, therefore the variance in reaching targets did not impact reaching strategy. Adults were filmed in one testing session in a kinesiology laboratory at the University of Lethbridge. Adults completed five reaching trials with their dominant (right) hand as they reached for small food item. Small food targets were chosen as the reaching targets of adults because a comparison of adult reaching to small food targets and

larger toys revealed no differences in hand trajectory, hand preshaping, or object placement into the mouth. The only exception was grasping, as the objects were grasped using a whole hand precision grasp (i.e. tips of three or more digits) (present thesis).

After each filming session, one researcher (LRS) viewed the infant tapes to ensure the parent(s) were following the filming procedures set out in the protocol (see below). The parents were contacted two days prior to the next scheduled video-recording session to remind them to film their child and to remind them to follow the agreed upon video-recording procedures for the age of their child. The infants were filmed for a minimum of ten minutes or a minimum of twenty successful reaches (i.e. grasp and place the target into the mouth).

Filming Instructions

In order to maintain standard video-recording procedures, one researcher (LRS) met with the parents and completed the first video-recording session with the parents to instruct them on how to film their child, which toys/food to use, and how to present the toy/food to the infant to elicit grasping.

The parents were given a set of written instructions, which detailed the procedure, the dates to film their child, what toys/food to use, and how to present the toys/food to the child. The parents had to agree to follow the written procedures to be included in the study. In brief, the parents were asked to select five to ten toys (the infants personal toys) that would serve as the “toy targets” for the early filming

sessions (e.g., 6 months to 9 months of age). Thus, the infants reached for the same set of toys in each of the seven filming sessions (6 months to 12 months). The toys were required to be small (wrist rattle) to medium (shaker rattle) sized to ensure that the object could be grasped by one hand. The parent chose one of the ten toys and presented the toy at arms length, in front (midline) of the infant. Once the infant grasped the toy, the parent loosened their grip so that the infant could withdrawal the toy to the mouth for oral exploration. At 10 months of age, the infants then reached for small food items. Parents were instructed to have their child reach for Cheerios™ or Fruit Loops™, food items that could elicit precision grasping. The seating apparatus was adapted to each of the two grasping targets:

Reach-to-oral exploration: Six- to nine-months-old infants were seated in a neck and back supportive chair, with the hands and arms free to grasp and manipulate objects, see Figure 1A. The parent held the target toy at an approximate distance of the infants arm's length at the midline of the infants body. The infant reached towards the toy, grasped the toy with the hand(s), and withdrew the toy to the mouth for oral exploration. The trial ended when the toy was placed into the mouth. Once the target was taken from the mouth, the parent removed the toy and a new toy was offered to initiate a new trial. Although toys are not a “food item”, infants systematically bring grasped objects to their mouth for oral exploration (Rochat, 1989; Piaget, 1952). Target toys were selected depending on the infants' interest and motivation. For example, at six months of age, infants reached for wrist rattles, and at eight months of age, infants reached for small animals. Because the target toys were the infants' personal toys, a familiarization phase was not necessary to habituate the infant to the toy.



Figure 1. Method: A) 6-to-9-month-old infants are seated in a back and neck supportive chair with their hands and arms free to grasp small toys (insert) that a parent holds in front of them. B) 10- to 12-month-old infants are seated in a highchair with an attached tray. A food item (insert) or small toy is placed on the food tray. C) Adults are seated in a chair with their feet flat on the floor. A food item (insert) is placed on a pedestal.

Reach-to-eat: Ten- to twelve-months-old infants were seated in a high chair with the tray table attached, with the hands and arms free to grasp and manipulate objects, see Figure 1B. The parent placed a small food item (e.g., Cheerios™) or small toy on the high chair tray. The infant reached towards the food item/small toy, grasped it with the hand, and withdrew it to the mouth for eating/oral exploration. The trial ended when the food item was released into the mouth and the hand was carried away from the mouth and held in a resting position or the small toy was brought to the mouth for oral exploration. The parent then either placed a new food item on the tray to initiate a new trial or removed the toy from the mouth and placed a new toy on the tray.

Adults. Adults were seated in a comfortable upright position, with their feet flat on the floor, see Figure 1C (de Bruin et al., 2008). A self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach

amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° extension) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion). The adults were instructed to reach for food with their dominant hand. Each testing trial was initiated with a verbal "ready" signal, immediately followed by a verbal "go" signal as a permissive cue to start the trial at their leisure. Each trial concluded following successful placement of the food item in the mouth and the return of the reaching hand to its start position on the lap. The experimenter then placed a new food item on the pedestal to initiate a new trial. The experimenter maintained a casual relationship with the subjects, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition.

Skilled Reaching Rating Scale

The Skilled Reaching Rating Scale is based on a description of reaching derived from a conceptual framework using Eshkol-Wachman Movement Notation (EWMN; Eshkol & Wachman, 1958; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998; Teitelbaum, Benton, Shah, Prince, Kelly, & Teitelbaum, 2004). This notation system has been adapted for the study of human reaching (Foroud & Whishaw, 2010; 2012; Whishaw et al, 2002). In brief, EWMN is designed to express relations and changes in relation between the parts of the body. The body is treated as a system of articulated axes (i.e. body and limb segments). A limb is any part of the body that either lies between two joints or has a joint and a free extremity. These are imagined as straight lines (axes), of constant length, which move with one end fixed to the centre of a sphere.

An important feature of EWMN is that the same movements can be described in several polar coordinate systems. The coordinates of each system are determined with reference to the environment, to the body midline, and to the next proximal or distal limb or body segment. By transforming the description of the same behaviour from one coordinate system to the next, invariances in that behaviour may emerge in some coordinate systems but not others. Thus, the behaviour may be invariant in relation to some or all of the following: the subject's longitudinal axis, gravity, or body-wise in relation to the next proximal or distal segment.

The topography of the reach-to-eat movement has been standardized using healthy young and old adults (Sacrey, Clark, & Whishaw, 2009), and previously applied to pathological adults with Huntington's disease (Klein, Sacrey, Dunnett, Whishaw, & Nikkhah, 2011), Parkinson's disease (Sacrey et al., 2009; Sacrey, Travis, & Whishaw, 2011), and stroke (Foroud & Whishaw, 2010). The movement is divided into seven components. In brief, the seven components of the reach-to-eat movement are:

- 1) *Orient*: subjects moves the head and eyes in order to visually fixate the target prior to reach onset and visually disengage the target at grasp.
- 2) *Lift*: hand is lifted and supinated towards the midline of the body as the digits close and semi-flex
- 3) *Advance*: hand is carried towards the target and stops above the target
- 4) *Pronation*: hand pronates over target item and digits shape to target size
- 5) *Grasp*: the target is grasped using a pincer grasp (thumb and index)
- 6) *Supination*: the hand rotates immediately after grasp of target and again as target approaches the mouth

- 7) *Release*: the target is released into the mouth and the hand is returned to its start position

The seven components are further divided into subcomponents, giving a total of 22 subcomponents (for a complete description, see Table 1). The coding scheme was developed to score adult reaching, both in healthy and pathological populations. As such, the developmental trajectory of reaching can be scored based on infant performance relative to healthy adult performance. For rating, a score of “0” is given if the movement is present and resembles the adult construct, a score of “0.5” was given if the movement was present, but differs from the adult construct, and a score of “1” was given if the movement was absent. Thus, the lower the score, the better the quality of the movement relative to the adult movement (Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002).

Sampled Reaches

To standardize the reaches scored, only those reaches that resulted in the object being brought to the mouth without accompanying manipulation (play) following grasp were analyzed. These consisted of, by far, the majority of reaches recorded. The number of successful reaches completed by each infant at each time-point varied, as shown in Table 2. Three reaches from each session were analyzed; reach one from the beginning of the session, reach two from the middle of the session, and reach three from the end of the session, for a total of 168 scored reaches. This method also allowed for a statistical comparison of any learning/trial effect (comparability of the reaching strategies from the beginning of the session to the end of the session). The

three sampled reaches per time point per infant were scored using frame-by-frame playback, as per methodology used in previous studies (Sacrey et al., 2009; Whishaw et al., 2002; Melvin et al., 2005). The reaches were sampled from the recordings closest to each month marker (i.e., at exactly six months, seven months, etc.) as long as the infant was cooperative for that session. If the infant was not cooperative, the video-record from the next session was analyzed. Reaches performed by either the right or left hands were included in the analysis.

Table 2. Skilled Reaching Rating Scale

Component	Element	Sub-Element	Description
Orient	Orient	A	Head is moving freely then fixes on target at beginning of trial
		B	Eyes fixate target prior to movement of hand/reach
Transport	Lift	A	Initial hand lift due to flexion of the elbow
		B	Digits semi-flex
		C	Hand supinated approximately 30 degrees
		D	Tips of digits are brought towards the midline of the body
	Advance	A	Hand takes shortest path to target
		B	Hand stops directly above the target
		C	Trunk leans to the side opposite reach
	Pronation	A	Digits open and extend over the food target
		B	Knuckle on reaching hand forms horizontal line
		C	Elbow opens to full arm length as subject reaches
Grasp	Grasp	A	Thumb and index finger grasp food item
		B	Digits 3-5 remain still as grasp is executed
		C	Wrist extends to lift food item from platform
Withdrawal	Supination	A	Reaching hand supinates 45 degrees immediately after vertical lift
		B	Hand supinates another 45 degrees when in close proximity to the mouth
Release	Release	A	Finger tips contact lips for placement of food item in mouth
		B	Digits open to release food item into mouth
		C	Hand is placed on lap with fingers extended and palm down
		D	Trunk leans back towards midline
Disengage	Disengage	A	Eyes look away from target at tactile contact

Inter-rater reliability. The first study to standardize the Skilled Reaching Rating Scale for humans reported no significant difference between scores from four different raters (Whishaw et al., 2002). For the present study, three reaches per infant per time-point (N = 168 reaches) were scored by two investigators (LARS and JMK).

Inter-rater reliability was assessed using Pearson's r , resulting in $r = 0.916$, $p < 0.002$, suggesting high reliability. Thus, only the scores from one experimenter (LRS) were used in the analysis.

Table 2. Total number reaches for each infant at each time point measured

ID	6	7	8	9	10	11	12
LC	17	7	12	8	12	11	12
AH	36	18	11	14	14	25	20
KW	22	22	9	7	7	9	9
KG	15	14	18	17	32	15	45
GM	25	12	14	12	15	15	15
BB	31	31	50	22	13	11	11
KS	19	53	50	16	13	14	23
MA	32	29	20	23	12	20	28
TOTAL	197	186	184	119	118	120	163

Kinematic Analysis

A digital video camera was positioned in front of the infant or adult to record a frontal view of the participant from lower leg to head for video recording at 30 f/sec, with a shutter speed of 500 frames per second. The trial reaches were digitized using Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the moving points by cursor with an output of 30 Hz. The three reaches scored using the Skilled Reaching Rating Scale were digitized in order to create kinematic reconstructions of the reaches. A frame grabber was used to project each frame and manually digitize each chosen biomarker on the image (e.g. ulnar styloid process). The system enhances each of the half-frame (fields) and presents them separately, thus converting 30 frames/second video sequence into 60 frames/second. The computer program calculates the distance travelled, the velocity, and the acceleration of each point on the body that was digitized (per Field, Whishaw,

& Pellis, 1996; Pellis & Pellis, 1994; Whishaw, Pellis, & Gorny, 1992; Whishaw & Pellis, 1990).

Movement jerk. The ulnar styloid process (reach wrist) of the moving hand was digitized from five frames before the onset of movement of hand/arm movement to five frames after the food/toy was placed into the mouth to determine movement jerk (smoothness).

Hand rotation. The knuckle of the second and third digits (with a virtual horizontal line serving as the baseline to which hand rotation was measured) were digitized from five frames before the onset of hand/arm movement to five frames after the food/toy was placed in the mouth to determine hand rotation throughout the reach-to-eat movement.

Hand Use

All reach and grasp movements made by each infant at each time-point were scored for hand use. The grasps were coded as (1) bimanual: used both hand to reach for and grasp the target; (2) left-handed: used only the left hand to reach for and grasp the target; or (3) right-handed: used only the right hand to reach for and grasp the target. The proportion of each hand(s) used (i.e., bimanual, left, or right) compared to all other hand(s) used (i.e. frequency of one hand(s) used/frequency of all hand(s) used) were calculated for each infant at each time point and were compared in the analysis. All adults reached with their dominant right hand.

Inter-rater reliability. Hand use was scored by an experimenter (LRS) and a second individual blind to the study objectives. The blind rater scored 50% of all reaches ($N = 539$) for hand use preference using the criteria listed above. Inter-rater reliability was assessed using Pearson's r , resulting in $r = 0.801$, $p < 0.001$ for left hand use, $r = 0.855$, $p < 0.001$ for right hand use, and $r = 0.872$, $p < 0.001$ for both hands used, suggesting high reliability. Thus, only the scores from the experimenter (LRS) were used in the analysis.

Statistics

Repeated measures ANOVA was used to examine the changes in arm movement across the six months of study. Statistical Package for the Social Sciences (SPSS) v. 19 was used to run the repeated measures with an alpha of 0.05 as significant. Bonferroni corrections were used for all post hoc comparisons. To simplify post hoc comparisons, only ages 6-, 9-, and 12-month-olds were compared.

Results

The infants were able to successfully transport either their left or their right hand to the target, grasp the target, and withdraw and place the target into the mouth. Nevertheless, the quality of the reaching movement differed depending on the age of the infant. Six-month-old infants perform the movement quite poorly, with jerky trajectories, no hand and digit shaping, and no rotation of the hand. They visually orient towards the target for an increased duration, when compared to adults, prior to

hand movement onset. Nine-month-old infants showed smoother trajectories when transporting and withdrawing the hand, began to show hand rotation, but did not shape their digits for grasping. They visually orient towards the target just before hand movement onset. Twelve-month-old infants accurately reach towards the target, supinate the hand and pre-shape the digits to grasp the target using a precision grasp, and supinate their hand to bring the target to the mouth for eating. They also visually orient towards the target just before hand movement onset and disengage as the target is grasped, as do adults.

Details of these results will be described in two sections that summarize the Skilled Reaching Rating Scale and the kinematic analysis. The Skilled Reaching Rating Scale scored the infants on their ability and accuracy in performing the components of the reach, orienting their head and eyes, lifting their hand and shaping the digit of the hand in transport, shaping the digits to grasp, and withdrawing the hand to place the target into the mouth. Kinematic analysis quantified the ‘jerk’ (smoothness) of the reach-to-eat movement, as well as changes in hand rotation during the components of the reach-to-eat movement.

Skilled Reaching Rating Scale Score

Figure 2 summarizes the overall score from the Skilled Reaching Rating Scale between 6 to 12 months of age. Scores on the scale decreased at each successive time point until by 12 months, the scores of the infants were comparable to that of adults. This summary was supported by a 7 X 3 repeated measures ANOVA on total Skilled Reaching Rating Scale score using Age (6, 7, 8, 9, 10, 11, 12 months) and Trial (1, 2,

3) as the within subjects factors. There was a significant effect of Age ($F(6, 42) = 37.83, p < 0.001$), but no Trial ($F(2,14) = 1.38, p > 0.05$) or Age x Trial ($F(12,84) = 0.35, p > 0.05$) effects.

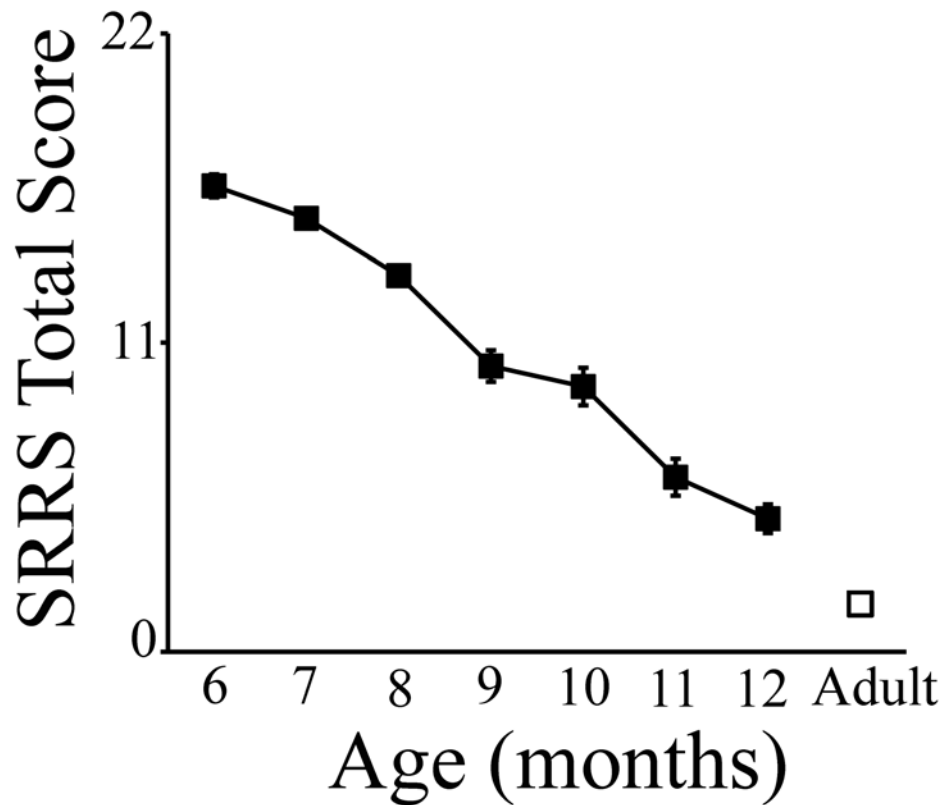


Figure 2. Skilled Reaching Rating Scale (SRRS) score (mean and standard error) for each age. The decrease in SRRS score with increasing age indicates more adult-like reaching movements.

Movement Sub-Component Analysis

The improvement in movement execution with age is supported by analysis from a 7 X 22 X 3 repeated measures ANOVA on each individual sub-component

(see Table 1) score. There was a significant effect of Age ($F(6, 42) = 37.78, p < 0.001$) and Sub-component ($F(21, 147) = 28.90, p < 0.001$), as well as an Age x Sub-component interaction ($F(126, 882) = 2.91, p < 0.001$). There was no effect for Trial ($F(2,14) = 1.39, p > 0.05$), Age x Trial ($F(12,84) = 0.35, p > 0.05$), Sub-component x Trial ($F(42, 294) = 0.80, p > 0.05$) or Age x Trial x Sub-component ($F(252, 1764) = 0.80, p > 0.05$). The features of the reaches of infants compared to adults are described in relation to the component movements of the reach:

1. *Orient.* Adults do not orient their head and eyes to the target until just before they initiate the reach but six-month-old infants continue to visually orient to the target well before they reach and continue to watch it as it is withdrawn to the mouth. Thus, six-month-old infants use visual monitoring to complete much of the reach-to-eat movement (Figure 3 I-A). Nine-month-old infants continue to visually orient to the target as it is grasped but disengage once the target is grasped (Figure 3 I-B). Twelve-month-old infants disengage, usually with a blink, as do adults, just as the target is grasped (Figure 3 I-D). Thus, visual guidance is excessive in young infants and conserved to the advance phase of the reach in older infants.

The age differences were confirmed with paired t-tests comparing the infants at ages 6-, 9-, and 12-months (Figure 3 II). There was no significant change in orienting the head and eyes towards the target between six and twelve months of age, there was a significant change in orienting the eyes away from the target with age, as nine- and twelve-month-old infants looked more similar to the adults than six-month-old infants ($p < 0.05$ and $p < 0.001$, respectively).

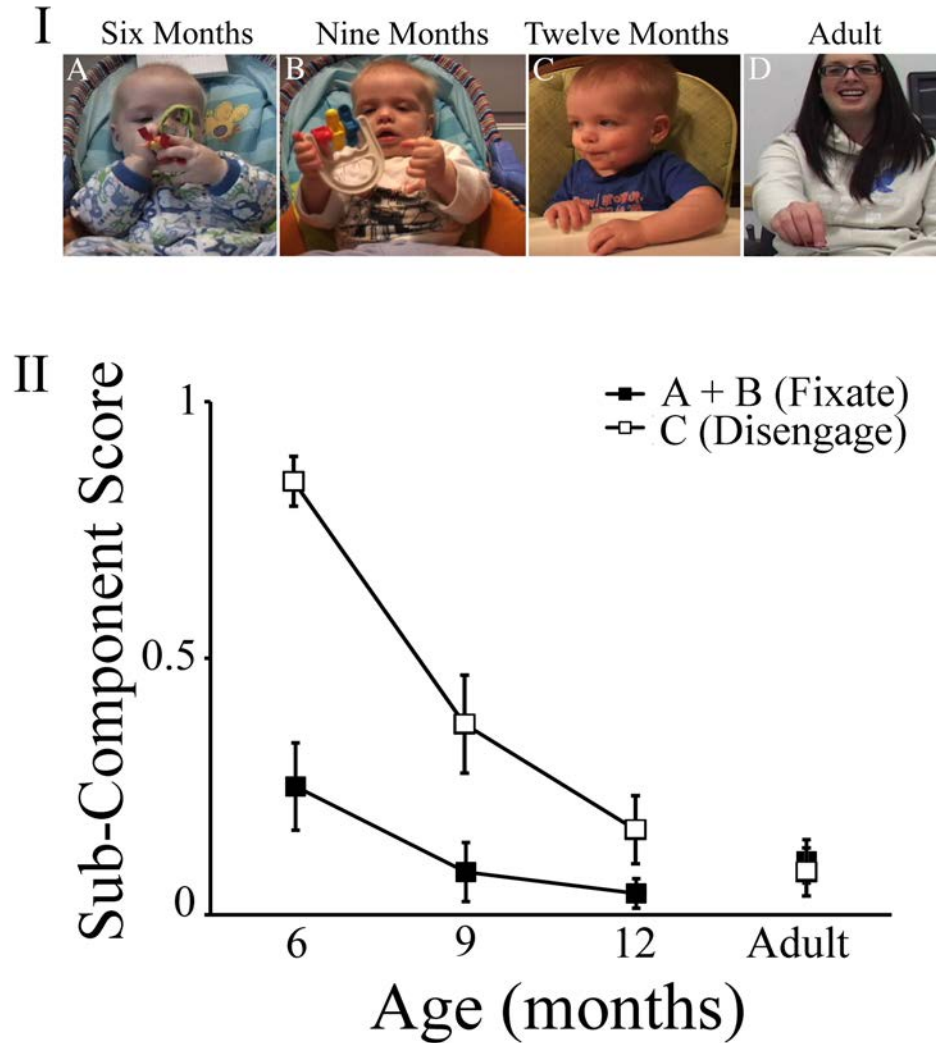


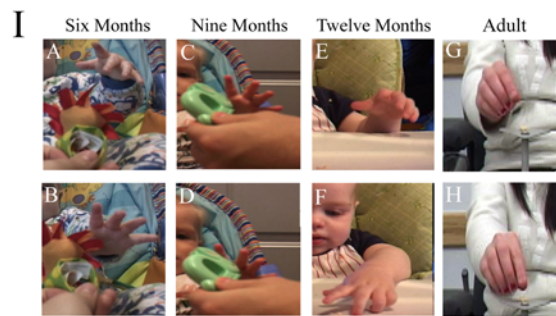
Figure 3. I. Visual disengagement in a (A) 6-month-old, (B) 9-month-old, (C) 12-month-old, and (D) an adult. II. Orient sub-component scores (mean and standard error) for A and B (head and eyes fixate) and C (disengage) for ages 6, 9, and 12 months and adults. Note the (A) 6-month-old visually follows the target to the mouth; (B) 9-month-old infants visually orient away from the target after it is lifted from the parents hand; (C) 12-month-old infants visually orient away from the target as the hand contacts it during grasp; and (D) adults visually orient away from the target as the hand contacts it during grasp.

2. *Transport*. To move their hand to the target, adults initiate the reach at the hand and flex their lower arm and elbow to lift the hand from the lap. They then semi-flex the digits and supinate the hand as the hand is lifted and the digits are held in a collected shape at the aiming position (Figure 4 I-G). They then extend the elbow to bring the hand toward the target, while at the same time the digits extend and pre-

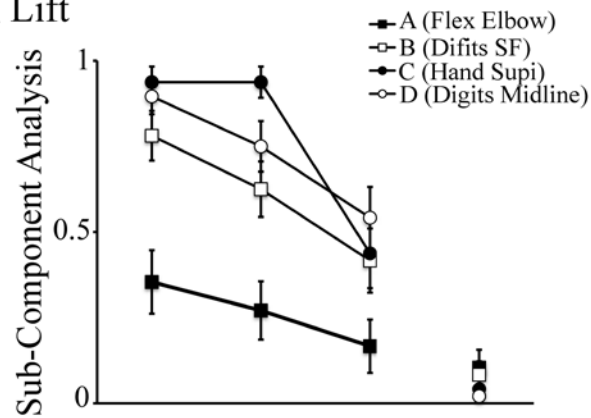
shape. At the completion of the aiming movement, and as the hand approaches the target, the digits over grasp and the hand pronates over the target (Figure 4 I-H). Lifting and transporting the limb is assisted by a shift of the trunk away from the reaching limb.

Six-month-old infants initiate the reaching movement through rotation of the shoulder to lift the hand from a substrate (Figure 4 I-A). The digits open and extend rather than semi-flex, and the hand does not supinate during transport. The trajectory of the hand is fragmented, moving in one plane and then the other (i.e. move in the x-plane followed by the y-plane) rather than simultaneously. End-point accuracy is poor as the hand does not orient towards the target and the digits do not open and extend in preparation for grasping (Figure 4 I-B).

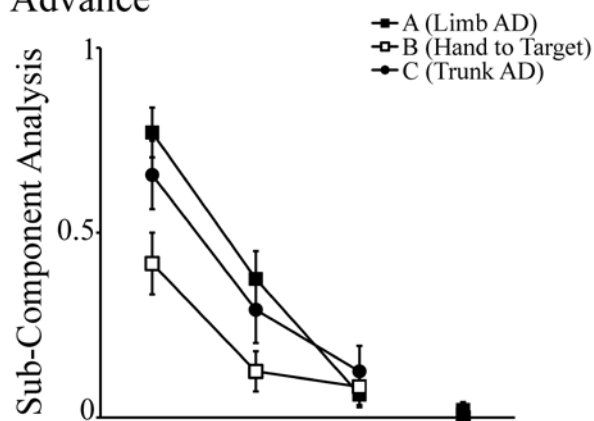
Nine-month-old infants lift the arm through flexion of the elbow, but continue to open and extend their digits with little hand rotation (Figure 4 I-C). Transport of the hand to the target is direct with minor corrections in hand trajectory and end point accuracy is improved (Figure 4 I-D). Preparatory hand shaping is not mature as the digits do not open and extend and the hand does not pronate prior to grasping.



II Lift



III Advance



IV Pronation

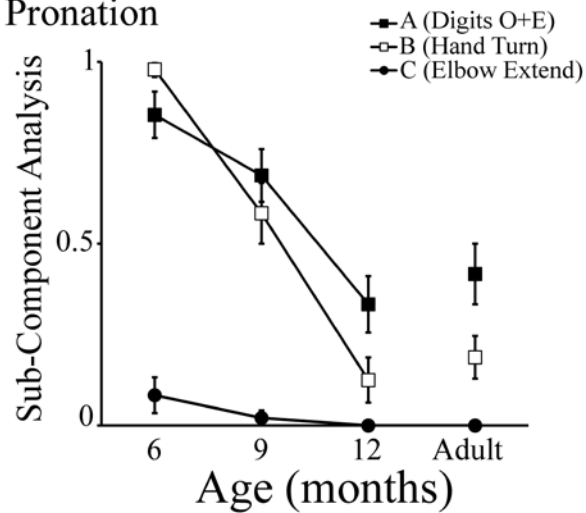


Figure 4. Advance. I. Representative photographs from a (A-B) 6-month-old, (C-D) 9-month-old, (E-F) 12-month-old, and (G-H) an adult. Advance scores (mean and standard error) for II Lift, III Advance, and IV Pronate. Note 6-month-old infants initiate the reaching movement through rotation of the shoulder to lift the hand with digits open and extended (A) and the hand ends off to the side of the target (B). 9-month-old infants lift the arm through flexion of the elbow with digits open and extended (C) and the hand ends above the target, just off to one side (D). 12-month-old infants lift their hand through flexion of the elbow with the digits semi-flexed (E) and the hand ends above the target (F). Adults lift their hand by flexion at the elbow and open their elbow to advance (G-H). (Previous page).

Twelve-month-old infants lift their hand from a substrate through flexion of the elbow and the hand supinates to collect the digits into a semi-flexed posture aligned to the midline of the body (Figure 4 I-E). The hand follows a direct path to the target, stops just above the target with digits extended and open, and the hand pronates over the for grasping (Figure 4 I-F).

The age differences were confirmed with significant paired t-tests on the sub element scores for lift (Figure 4 II), advance (Figure 4 III), and pronate (Figure 4 IV). With the exception of elbow opening, which was similar across ages, there were significant changes in other measures with 12 month infants differing little from adults.

3. *Grasp*. Adults use a precision grasp, generally using the thumb and index finger to purchase the target, generally with slight flexing of digits 3 through 5 accompanying the grasp (Figure 5 I-G). The wrist extends to lift the target from the pedestal (Figure 5 I-H).

Infant grasping patterns change with age. Six month-old infants purchase a

target using a whole hand grasp in which all digits are open and extended in a “fan-like” pattern and then close around the target at contact (Figure 5 I-A). The wrist does not extend to lift the target, but rather the hand pulls the target back and slides it from the parents’ hand (Figure 5 I-B). At nine months of age, infants continue to grasp the target using a whole hand grasp and still show little wrist extension (Figure 5 I-C-D). Twelve-month-old infants grasp the target using a precision grasp (Figure 5 I-E). The thumb and index finger purchase the target, digits three through five semi-flex as the grasp is completed and the wrist extends to lift the target from the tray (Figure 5 I-F).

These age-related changes were progressive (Figure 5 II). Twelve-month-old infants looked more similar to adults when grasping the target than six-month-old infants ($p < 0.01$), and when keeping digits three through five still while grasping ($p < 0.05$ and $p < 0.01$, respectively). Twelve-month-old infants looked more similar to the adult than nine-month-old infants when shaping digits three through five during grasp ($p < 0.01$). Nine- and twelve-month-old infants looked more similar to the adults when extending the wrist following grasp than did six-month-old infants ($p < 0.0167$).

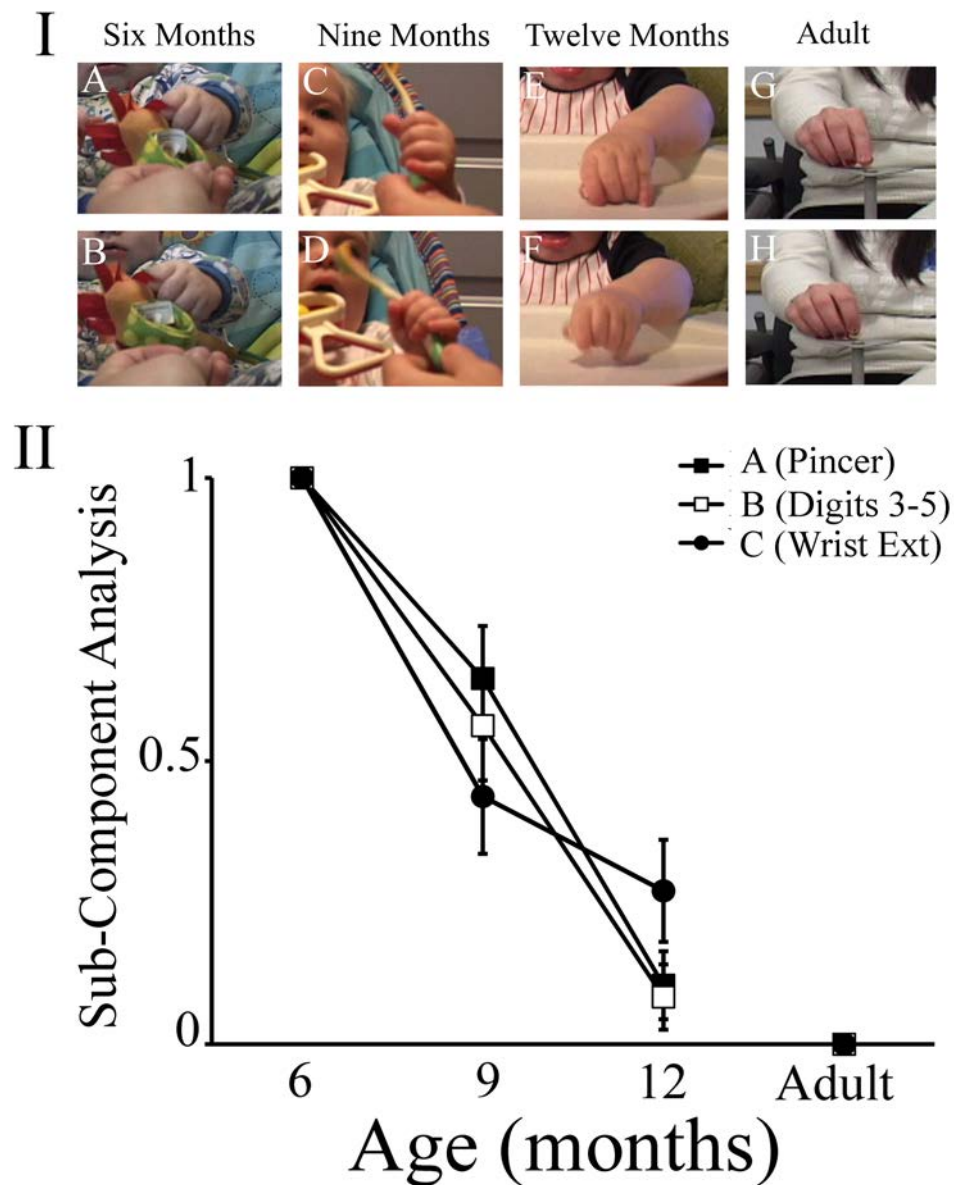


Figure 5. Grasp. I. Representative photographs from a (A-B) 6-month-old, (C-D), 9-month-old, (E-F) 12-month-old, and (G-H) an adult. II. Grasp sub-component scores (mean and standard error) for A (pincer), B (digits 3-5), and C (wrist extension) for ages 6, 9, and 12 months and adults. Note (A-B) 6-month-old infants purchase a target using a whole hand grasp and the hand pulls the target back and pulls it from the parents' hand. (C-D) 9-month-olds purchase the target using a whole hand grasp and pull toy from parents' hand. (E-F) 12-month-old infants grasp the target using a pincer grasp and the wrist extends to lift the target from the tray. (G-H) Adults grasp the target using a pincer grasp and the wrist extends to lift the target from the pedestal.

4. *Withdrawal.* Adults supinate the hand by about 45 degrees in supination I, as they lift the hand to initiate withdrawal (Figure 6 I-G) and they supinate by a further 45 degrees, supination II, to bring the target to the lips (Figure 6 I-H). As the hand withdraws, the trunk shifts to its starting upright position so that the lips meet the approaching hand.

Six-month-old infants do not supinate their hand immediately following lifting of the target from the parent's hand to place the target in the correct orientation, nor do they supinate the hand as the target nears the mouth (Figure 6 I-A-B). Additionally, the hand may drop after the target is lifted prior to being brought to the mouth. Supination improves progressively (Figure 6 C-H) until twelve months of age, when infants display both supination I and supination II.

The age related changes in supination were significant (Figure 6 II), as nine- and twelve-month-old infants looked more similar to the adults than did six-month-old infants at supination I ($ps < 0.001$) and at supination II ($ps < 0.001$). Twelve-month-old infants looked more similar to the adults than nine-month-old infants ($ps < 0.01$).

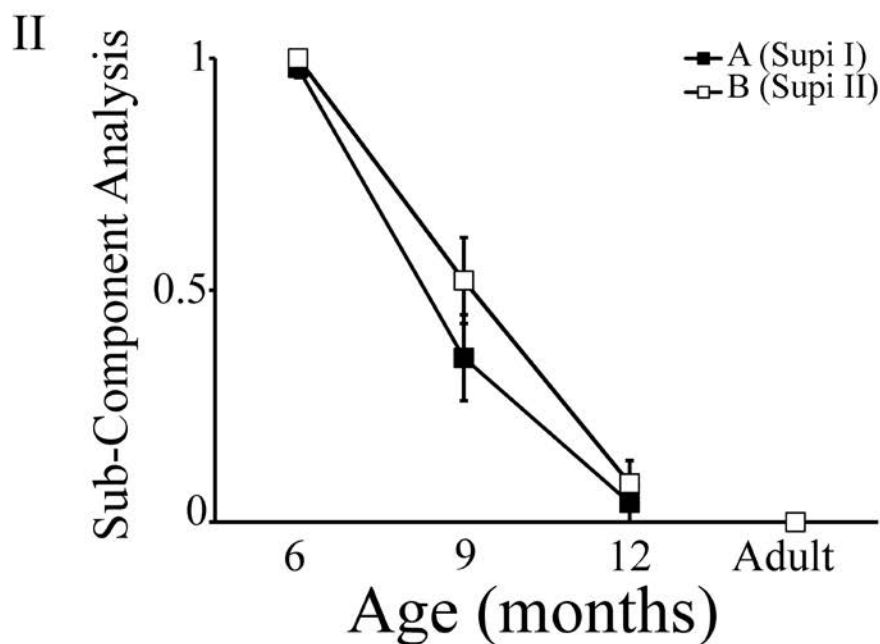
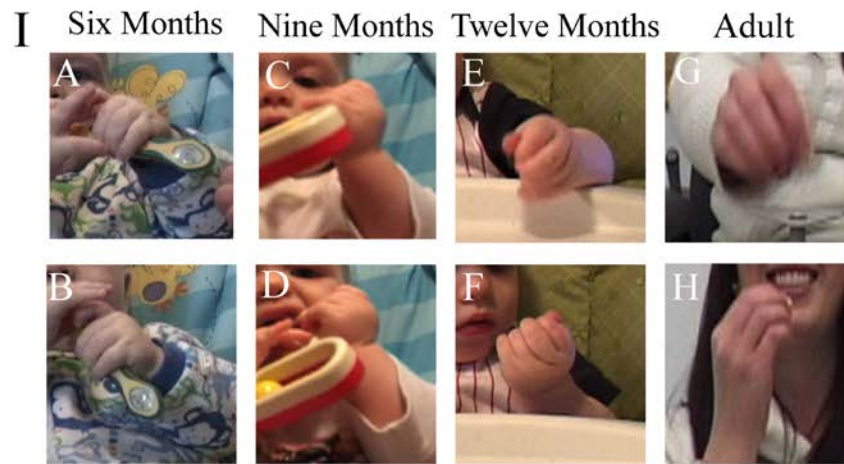


Figure 6. Withdrawal I. Representative photographs from a (A-B) 6-month-old, (C-D) 9-month-old, (E-F) 12-month-old, and (G-H) an adult. II. Withdrawal sub-component scores (mean and standard error) A (supination I) and B (supination II) for ages 6, 9, 12 months and adults. Note (A-B) 6-month-old infants do not supinate their wrist following lift of the target or as the hand nears the mouth. (C-D) 9-month-old infants show some supination of the wrist following lift of the target and as the hand nears the mouth. (E-F) 12-month-old infants supinate their wrist following lift of the target and as the hand nears the mouth. (G-H) Adults supinate their wrist following lift of the target and as the hand nears the mouth.

5. *Release*. Adults bring the food item to the lips and open the digits to release the food as the lips close to grasp the food item. After the food item is released, adults lower the hand and place it on the starting position on the lap (Figure 7 H).

The pattern of release of the target into the mouth changes with age. At six months of age, infants display an accuracy error when placing the target into the mouth as the target often hits the chin or cheek (Figure 7 I-A). Although the target is eventually placed in the mouth, infants do not open their digits and release the target, but rather continue to grasp the target as they manipulate it with their mouth (Figure 7 I-B). Infants will also take the target out of its mouth, look at it, and then place it back in their mouth again. By nine months of age, infants are more accurate at placing the target into the mouth, but continue to hold onto the target as they manipulate it with their mouth (Figure 7 I-C-D). The infants will also take the target out of the mouth, look at it, and then place it back in their mouth again. At twelve months of age, infants accurately place the target into the mouth, but may continue to keep the tips of their digits in their mouth for an extended period of time after it has been released (Figure 7 I-E-F). When the target is released, the hand may not lower but remains in the air near the head or off to the side of the body.

These age-related changes were significant (Figure 7 II). Nine- and twelve-month-old infants look more similar to the adults than six-month-old infants ($ps < 0.001$). Twelve-month-old infants looked more similar to the adult than nine-month-olds infants ($p < 0.05$). Nine- and twelve-month-old infants looked more similar to the adult when opening their digits to release the target into the mouth than six-month-old

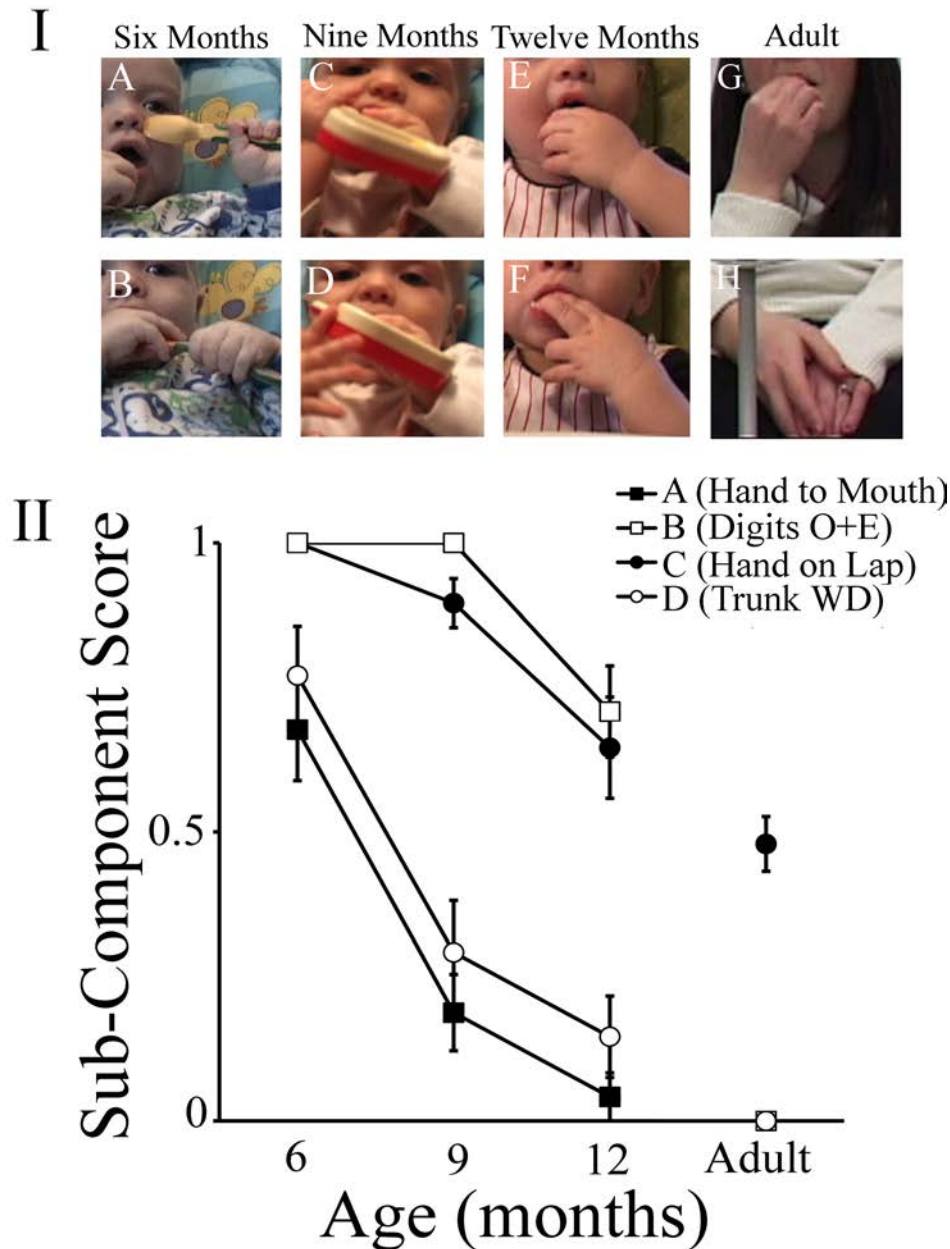


Figure 7. Release. I. Representative photographs from a (A-B) 6-month-old, (C-D) 9-month-old, (E-F) 12-month-old, and (G-H) an adult. II. Release sub-component scores (mean and standard error) for A (hand to mouth), B (digits open and extend), C (hand on lap), and D (trunk adjust) for ages 6, 9, 12 months, and adults. Note (A-B) 6-month-old infants touch the target to the cheek before it is placed in the mouth. (C-D) 9-month-old infants accurately place the target into the mouth, but continue to hold onto the target as they manipulate it with their mouth. (E-F) 12-month-old infants accurately place the target into the mouth, but continue to keep their digits in the mouth for an extended period of time after it has been released. (G-H) Adults accurately place the target into the mouth and return their hand to the start position on their lap.

infants ($ps < 0.05$). Twelve-month-old infants looked more similar to the adult construct when placing the hand in the start position than six-month-old infants ($p < 0.05$), and nine- and twelve-month-old infants looked more similar to the adult construct when adjusting their trunk back during withdrawal than six-month-old infants ($ps < 0.01$).

Kinematic Analyses

Movement jerk. Representative examples of movement jerk (smoothness) of six-, nine-, and twelve-month old infants, from movement onset to placement of the target into the mouth, are illustrated in Figure 8. A comparison of hand displacement and hand velocity illustrates the jerky (unsmooth) movement (Figure 8A), as well as an increased number of movement units (Figure 8B) for the reach-to-eat movement in six-month-old infants. By nine months of age, infants display less jerkiness (increase in movement smoothness) (Figure 8C) and a decreased number of movement units (Figure 8D) when completing the reach-to-eat movement. By twelve months of age, the reach-to-eat movement becomes quite smooth (Figure 8E), with two movement units (Figure 8F), characteristic of adult reach-to-eat movements.

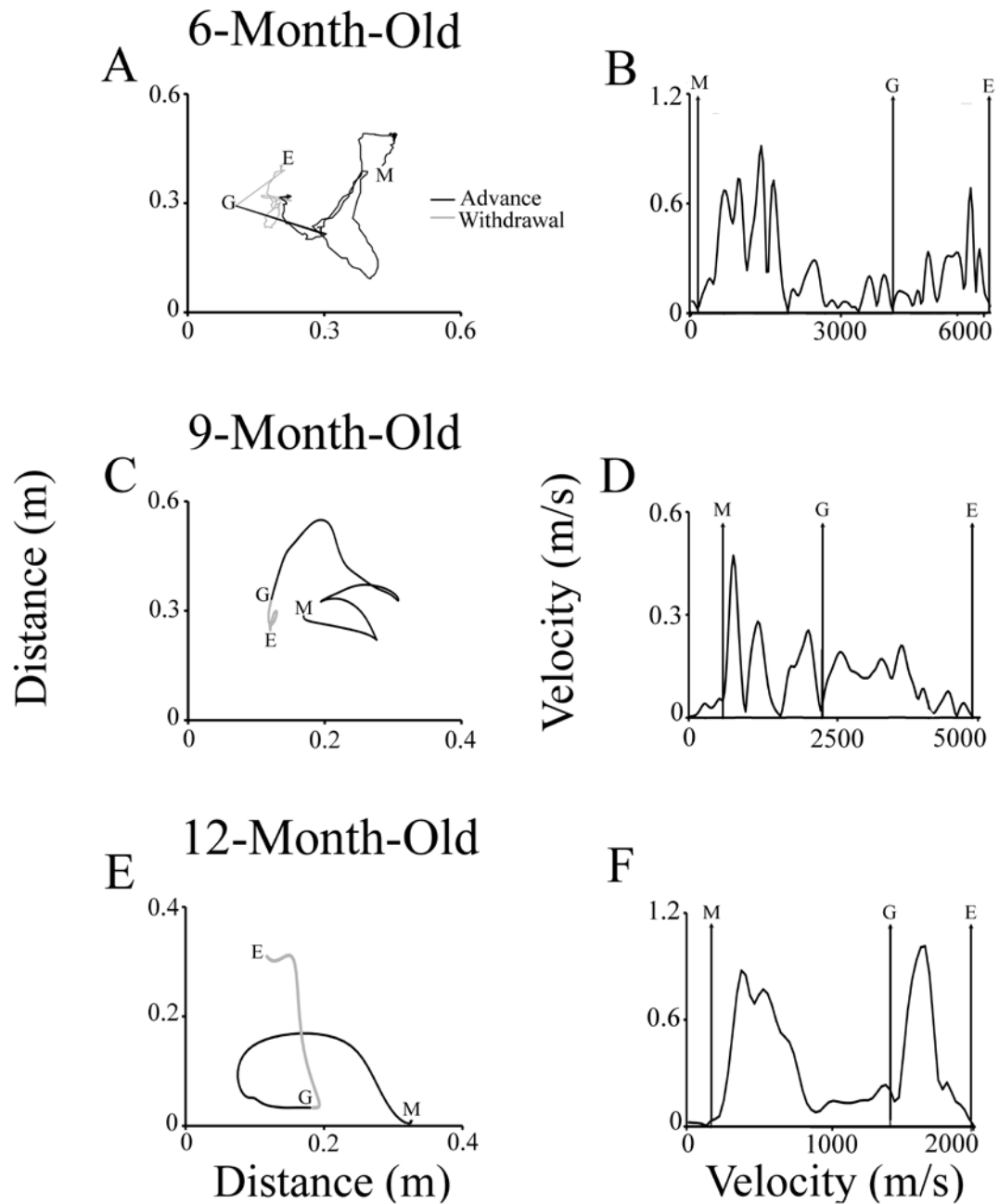


Figure 8. Representative kinematics of hand trajectory (A, C, E) and velocity (B, D, F) for infants aged 6, 9, and 12 months. Hand trajectories show a reduction in movement jerk and velocity profiles show a reduction in movement units, with 12-month-old infants demonstrating the smoothness characteristic of adult reach-to-eat movement. M = movement onset, G = grasp, E = place in mouth (eat).

Hand rotation. The change in hand rotation with age is illustrated in Figure 9. As shown in Figure 9A, six-month-old infants do not show variance in hand rotation until the target is withdrawn towards the mouth. By nine months of age, infants begin to demonstrate hand rotation, particularly during pronation of the hand over the target prior to grasping and as the hand is withdrawn towards the mouth (Figure 9B). At twelve months of age, infants show hand rotation that is similar to adults (Figure 8 C-D).

The change in hand rotation with age is confirmed by a 7 X 6 X 3 repeated ANOVA on hand angle with Age (6, 7, 8, 9, 10, 11, 12 months of age), Component (Start, Lift, Pronation, Grasp, Supination I, Supination II) and Trial (1, 2, 3) as the within subjects factors. There was a significant effect of Age ($F(6, 42) = 4.76, p < 0.001$) and Component ($F(5,35) = 122.94, p < 0.001$), and an Age x Component ($F(30,210) = 1.78, p < 0.01$) interaction. There was no significant effect of Trial ($F(2,14) = 0.36, p > 0.05$) or Age x Trial ($F(12,84) = 0.66, p > 0.05$) and Component x Trial ($F(10,70) = 0.81, p > 0.05$) interactions. Ages six-, nine-, and twelve-months were compared using paired t-tests. Twelve-month-olds show a lower angle of rotation at 'start' compared to six-month-olds ($p < 0.05$), a lower angle of rotation at 'lift' for twelve-month-olds compared to six-month-olds ($p < 0.01$), a lower angle of rotation at 'pronation' for nine- and twelve-month-olds compared to six-month-olds ($p < 0.05$ and $p < 0.001$, respectively), and a lower angle of rotation at 'grasp' for twelve-month-olds compared to six-month-olds ($p < 0.001$).

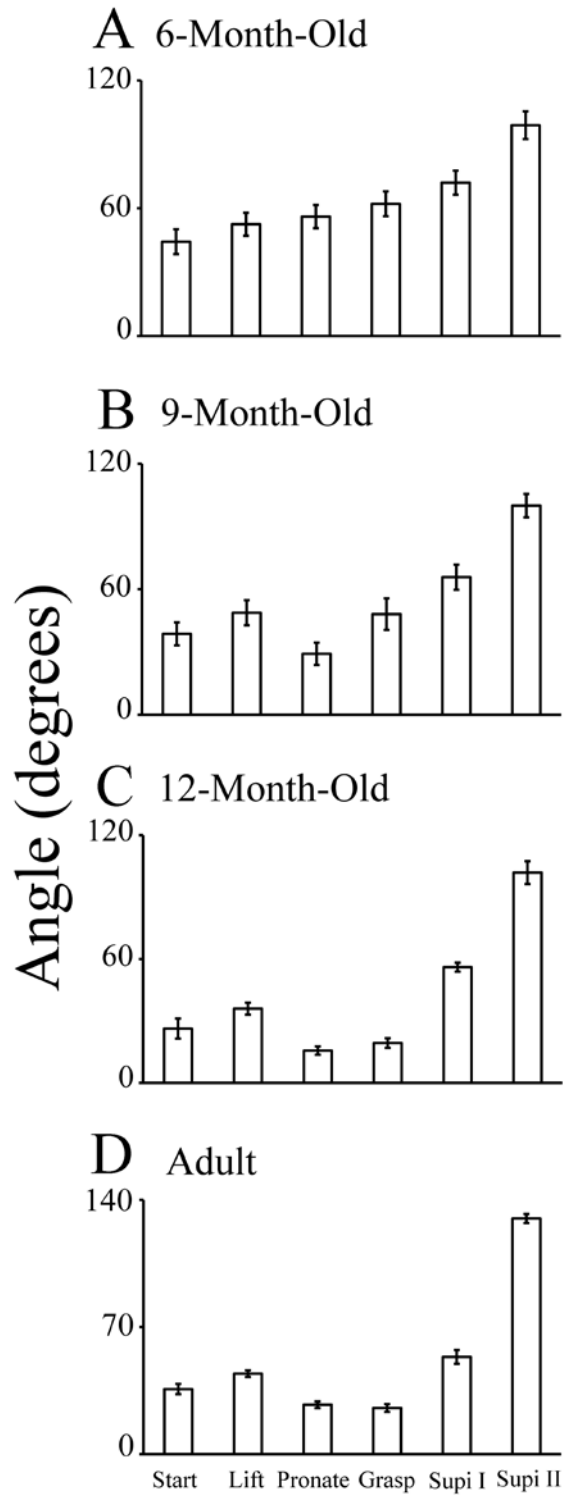


Figure 9. Hand rotation (mean and standard error) for ages (A) 6, (B) 9, (C) 12 months, and (D) adult. Note that (A) 6-month-old infants show little change in hand orientation when completing the advance and grasp components of the reach. (C) 12-month-old infants show changes in hand orientation resembling that of the adult (D).

Hand Use

Infants initially alternated between bimanual and unimanual grasping, and then progressed to unimanual hand use, featuring increased use of the right hand. These findings are supported by a 7 X 3 repeated measures ANOVA on hand use using Age (6, 7, 8, 9, 10, 11, 12 months) and Hand (bimanual, left, right) as the within subjects factors. There was no effect of Age ($F(6, 42) = 1.20, p > 0.05$), but there was an effect of Hand ($F(2, 14) = 7.01, p < 0.01$) and an Age x Hand interaction ($F(12, 84) = 3.44, p < 0.001$). To simplify follow-up comparisons, only ages 6, 9, and 12 months were compared. There was no significant difference in hand use preference for bimanual, right-hand, or left-hand grasping at 6-months of age. At 9 months of age, infants grasped using the right hand more than the left hand and bimanually ($ps < 0.05$), and at 12 months of age, infants grasped using both their right ($p < 0.01$) or left hand ($p < 0.05$) more than bimanual grasping.

Figure 10 illustrates the changes in hand use preference when grasping. As shown in Figure 10A, the incidence of bimanual grasping decreases significantly from 6 months of age to 9 months of age ($t(7) = 2.83, p < 0.05$) and non significantly from 9 to 12 months of age ($t(7) = 1.95, p > 0.05$). Figure 10B shows the incidence of right-handed grasping increases from 6 months to 9 months of age ($t(7) = 4.82, p < 0.01$) and remains relatively stable thereafter ($t(7) = 0.29, p > 0.05$). Figure 10C shows that left-handed grasping does not change from 6 to 12 months of age ($t(7) = 0.65, p > 0.05$). Figure 10D illustrates that overall there are more right-handed grasps than bimanual grasps ($p < 0.01$) with a trend for more right-handed grasps than left-handed grasps ($p = 0.07$).

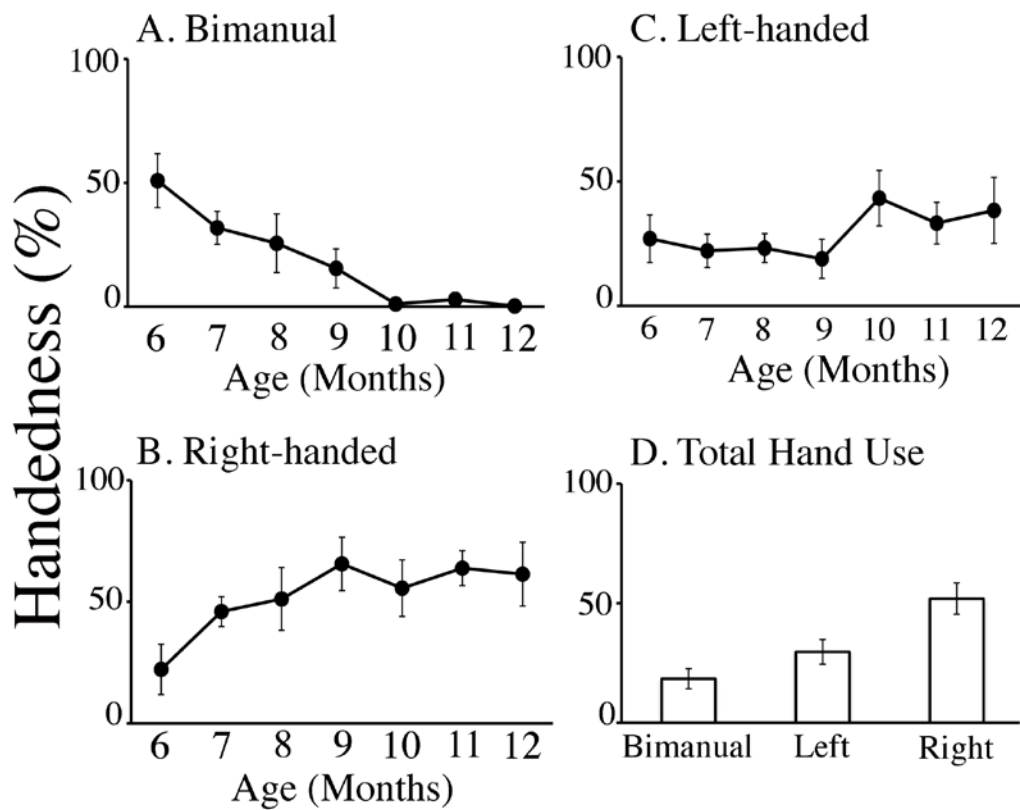


Figure 10. Hand use preference by infants aged 6 to 12 months when grasping. (A) Bimanual; (B) Right hand; (C) Left hand; and (D) Overall hand use preference. Note the decrease in bimanual reaching from 7 months, and the increase in right handed reaching by 12 months of age.

Discussion

While many studies have documented reach-to-eat hand use in infants, this study provided the first longitudinal description of the rotational movement and limb trajectories of reaching. Infants were video-recorded at their homes from six months of age to twelve months of age as they reached for toys and food items to grasp and bring to the mouth. Movements were rated using a scale based on adult reaching. Over the 6 month observation period, the infants: (1) gradually developed mature

rotational movements of the hand and hand shaping movements, (2) integrated the movements of the hand with trunk, head, and arm movement, and (3) became increasingly smooth and accurate in targeting objects and the mouth, and increasingly used a preferred hand. Taken together, the findings show that the development of hand movements involves the gradual integration of rotational movement of limb segments, hand accuracy, and lateralization.

The method of the present study utilized the ethological approach of behavioural sampling of a designated behaviour, video recording the behaviour, and examining the behaviour frame-by-frame to document its development (Wallace & Whishaw, 2003). Parents filmed their infant at seven time-points to obtain 20 incidences of skilled reaching behaviour for each time point. This method produced a large sample of skilled reaching acts at each sampled age from all of the infants. Age appropriate targets (to avoid choking hazards) consisted of toys for infants between six and nine months of age and small food items or small toys for infants between ten and twelve months of age. Although a detailed inter-subject analysis was not made, there were no obvious gross differences in the development of the behaviour in different subjects. Thus, the findings from the subjects were pooled at designated developmental ages. This procedure allowed for the capture of behaviour as it unfolds as an act and over time, avoided placing infants in a structured experiment, and produced a large data sample.

A number of caveats must be made with respect to the procedures used. For adults, a consistent posture for reaching was obtained, with the subjects sitting in a chair. This posture may allow more freedom of movement, thus more clearly

revealing rotatory movements and movement accuracy. Infants, especially young infants, were usually partially supine and supported so that their movements may have been constrained. Nevertheless, it is postulated that the movement components analyzed are sufficiently robust to minimize this drawback. Additionally, the observational method has disadvantages, as frame-by-frame analysis of data is time-consuming and subject to scoring error. Nevertheless, it was found that inter-rater reliability was very high and the results from kinematic analysis supported the results from behavioural scoring. Finally, the sample was small and drawn from a homogenous ethnic group, but the pattern of development had a very high inter subject reliability.

Hand use preferences were incidentally collected from the data and consistent with findings of a number of previous studies (Van Hof, Van der Kamp, Caljouw, & Savelsbergh 2005; Fagard, 2000; Bresson, Broughton, & Moore, 1977), confirming that the subject pool was representative. That is, infants initially matured from bimanual to unimanual grasping featuring increased use of the right hand. It is important to note however, that the approximate 50% of bimanual grasps in the earlier age groups may be related to the large size of the targets (in comparison to a small food item) and the nearly exclusive use of unimanual grasping at 12 months of age may be related to the small size of the targets. The inconsistencies in findings related to both bimanual hand use and hand preference in a number of studies is in large part due to the difficulty in standardizing the reaching targets across developmental age (Corbetta & Thelen, 1996; Corbetta, Thelen, & Johnson, 2000; Fagard, 2000; Ferre, Babik, & Michel, 2010). Nevertheless, in the present study, object size was unlikely to have been the sole determinant factor in influencing hand use and hand shaping

because bimanual reaches decreased at each successive time-point even though infants reached for the same target objects.

The infants were surprisingly inaccurate both in directing their hand to a target and in bringing the target to their mouth at the earliest time points. At six months of age, the hand followed a jerky path to the target, often moving in the x then y plane, with the hand ending awkwardly to the side of the target (von Hofsten, 1991; Berthier, Clifton, McCall, & Robin, 2010; von Hofsten and Lee, 1982; Mathew & Cook, 1990; Fallang, Saugstad, & Hadders-Algra, 2000). The similar inaccuracy in withdrawing the target to the mouth, in which the infant often contacts the cheek or chin before adjusting the target to the area of the mouth, has not been previously noted. Accuracy of both grasping and withdrawal improved gradually, such that by twelve months of age, the hand followed a direct path to the target, and a direct path with the target to the mouth, as revealed by kinematic analysis. The gradual improvement in movement accuracy with age is probably related to the maturation of sensory and motor control (Rocha, Silva, & Tudella, 2006) but is also likely affected by experience with the reaching in the inter-test intervals (Martin, Friel, Salimi, & Chakrabarty, 2007; Martin, Choy, Pullman, & Meng, 2004; Bower, 1974).

Relative to adult reaching, the sub-components of the initial reaching movements were quite simple, featuring a paucity of rotational and hand shaping movements. Previous studies have documented some of the features of infant reaching described here, e.g., the open “fan-like” configuration of the hand (McGraw, 1941), lack of hand shaping, pronation, and supination characteristic of adult grasping (Lockman, Ashmead, & Bushnell, 1984), and the later maturation of hand pronation

(Fagard, 2000), and hand shaping (von Hofsten et al., 1984; Berthier et al., 1999). Some features of the development of infant reaching have not been described, including hand collection and rotation during advance and supination during withdrawal. The strength of the present study resides in the use of a formal, standardized scale, the explicit comparison to adult movement, and the documentation of the time line of movement development. The findings of the study show that the scale is sensitive to age-related changes and suggest that the scale could be usefully applied not only to descriptions of normal development, but also to developmental abnormalities (Zwaigenbaum, Bryson, Rogers, Roberts, Brian, & Szatmari, 2005; Coluccini, Maini, Martelloni, Sgandurra, & Cioni, 2007).

Visual orientation on the target in infants has not received the attention accorded to adult reaching, in which there is a tight coupling of visual engagement with the initiation of hand transport and disengagement with grasping (de Bruin et al., 2008). In the present study, the precise timing of eye movements towards and away from the target were not measured, however the eye movements were clearly indicated on the video record. It was found that there was a progressive development of this coupling of visual orientation on the target for hand advance and grasping. The younger infants displayed exaggerated visual engagement with a target both before and after grasping. By twelve months of age, the infants displayed an adult pattern of engagement on the target as the reach was initiated and visual disengagement as the target is grasped. The observations made here confirm some earlier reports that infants gaze at objects before reaching for them (Bushnell, 1985; Bower, 1974; Bruner et al., 1972; McCarty, Clifton, Ashmead, Lee, & Goubet, 2001), and that younger infants gaze at objects for a longer duration than older infants (Ruff, 1986).

Future experimentation could measure the eye movements during reaching using eye-tracking and/or kinematic software. Nevertheless, the current study described the development from increased visual orienting of the target to a coupling of visual orientation on the target during hand advance, suggesting the adult pattern has a gradual development, paralleling the development of rotational and hand shaping movements.

The findings of the present study confirm many previous reports that there is a gradual development of adult-like reaching during the second half of the first year of life (McGraw, 1941; Twitchell, 1970; Wimmers, Savelsbergh, Beek, & Hopkins 1998; Bower, 1974) but the present work also suggests that the development of reaching is more complex than has been appreciated. First, this study integrates the process of visual orientating on the target to the movements of advance, grasping, and withdrawal. Second, this study provides the first complete description of the withdrawal movement, which, on the basis of previous evidence, has received most attention in foetuses and newborns (Piaget, 1952; Rochat, 1989). Third, the present study confirms that although infants develop independent digit movements (“hand-babbling”) before five months of age, and engage in self-grasping before six months of age (Wallace & Whishaw, 2003), the same digit movements do not become evident in visually controlled reaching until ten to twelve months of age. Taken together, this evidence suggests that there are a number of preparatory stages of skilled reaching, such as the early developing withdrawal movement and “hand-babbling”, that only later become mature movements under visual guidance (Trevvarthen, 1984).

In conclusion, this longitudinal study using frame-by-frame video analysis and kinematic analysis of accuracy, movement components, and visual orientation shows that the development of reaching involves lateralization and widespread integration of limb segments and sensory control and is gradual. Thus, over the developmental age examined, there is ample room for the behavior to be shaped both by experience and by nervous system maturation (Courtine et al., 2007; Corbetta & Snapp-Childs, 2009; Lobo & Galloway, 2008;). The anatomical understanding of the development of the corticospinal system in humans in mediating independent digit movements in grasping is not fully understood (Kuypers, 1981; Lemon, 2008; Yakovlev, & Lecours, 1967). Nevertheless, the retraction of symmetrical bilateral corticospinal projects and the maturation of the crossed projection is likely related in part to the maturation of the reaching movement components described here (Chakrabarty, Friel, & Martin, 2009; Martin, 2005; Martin et al., 2007; Martin et al., 2004). Additionally, the movements are also likely dependent upon the maturation of cortical motor systems (Graziano, 2006; Graziano, Aflalo, & Cooke, 2005) and of the visual and somatosensory guidance, as might be provided by the dorsal and ventral visual and somatosensory streams that project through parietal and temporal cortex respectively (Goodale and Milner, 1992). Finally, the formal rating scale and the developmental timeline of the reach-to-eat movement described here might be useful for assessing abnormalities in development (Zwaigenbaum et al., 2005; Coluccini et al., 2007).

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Chapter 3

Development of visual and somatosensory attention of the reach-to-eat movement in human infants aged 6 to 12 months

Abstract

The reach-to-eat movement is a natural act in which an object or food item is grasped and transported to the mouth and it is one of the earliest forelimb behaviors displayed by human infants. In adults, there is a tight coupling between visual attention and the advance phase of the reach-to-eat movement and somatosensory attention and the withdrawal phase of the reach-to-eat movement. The present study examined how the relationship between sensory attention and movement develops in infancy. In a longitudinal study, eight infants, aged six months to twelve months, and twenty adults reached for familiar inanimate objects and food items. Hand and eye movements and accuracy were measured using manual, frame-by-frame kinematic analysis. The results show that there was a gradual increase in sensory coupling of vision to hand advance and somatosensation to hand withdrawal, such that by twelve months of age, infants approximated the adult pattern. Performance was likely the result of the concomitant maturation of the arm, hand, and rotatory movements, the development of precision grasping, and the improving targeting accuracy both for grasping and placing the target into the mouth. The results are discussed in relation to the idea that online sensory attention and motor control for reaching develops in parallel.

The reach-to-eat movement, in which a hand advances to grasp a target to bring it to the mouth, is a natural act and is displayed in a number of forms by developing infants. Foetuses will bring a hand to the face and insert a thumb into the mouth (de Vries, Wimmers, Ververs, Hopkins, Savelsberg, & van Geijn, 2001; Hepper, Shahidullah, & White, 1991; Sparling, Van Tol, & Chescheir, 1999). Newborn infants will automatically grasp objects that have been placed in the hand (Twitchell, 1970) and will bring grasped objects to the mouth (Rochat, 1989; Rochat & Senders, 1991; Whyte, McDonald, Baillargeon, & Newell, 1994). By four months of age, infants will reach for distal objects that are then nearly always brought to the mouth, either for haptic exploration or for eating (Butterworth & Hopkins, 1988; Hopkins, Janssen, Kardaun, & van der Schoot, 1988; Piaget, 1952). By ten to twelve months of age, hand grasps approximate those of adults in that small items are purchased using precision grips, including the pincer grasp (Sacrey, Karl, & Whishaw, 2012; Touwen, 1976; von Hofsten & Fazel-Zandy, 1984; White, Castle, & Held, 1964). Studies of the sensory control of reaching movements suggest that they are influenced by somatosensory guidance in early infancy but gradually come under visual control. To illustrate, infants are not able to use visual information of the target to adjust hand orientation prior to contact until seven to nine months of age (McCarty, Clifton, Ashmead, Lee, & Goubet, 2001). At earlier ages, removal of visual feedback of the reaching hand has no effect on reach kinematics (Clifton, Rochat, Robin, & Berthier, 1994; McCall, Robin, Clifton, & Berthier, 1994; Robin, Berthier, & Clifton, 1996), as orientation to grasp the target occurs only after tactile contact is made (Lockman, Ashmead, & Bushness, 1984; Newell, Scully, McDonald, & Baillargeon, 1993; Witherington, 2005). It is not until one year of age that removal of visual feedback of

the reaching hand results in similar impairments in infants and adults (Berthier, Clifton, McCall, & Robin, 1999; Berthier & Carrico, 2010; Carrico & Berthier, 2008).

Despite this confluence of evidence that the sensorimotor control of the reach-to-eat movement achieves adult status by the first year of life, it is not known whether the patterning of visual and somatosensory control of reaching is developed at this time. Biometric analyses of the adult reach-to eat movement shows that sensory control of the movement is tightly coupled to the advance and withdrawal phases of the movements respectively (de Bruin, Sacrey, Doan, Brown, & Whishaw, 2008; Sacrey, Travis, & Whishaw, 2011). The target food item is visually fixated just prior to initiation of the advance phase towards the target and is visually disengaged, usually with an eye blink and orientation of the face away from the target, as the hand contacts the food item to initiate grasping. Hand withdrawal, in which a hand is directed to the mouth to release the food item, is thus guided by somatosensation. This dual sensory control of the reach-to-eat movement is confirmed by studies using visual occlusion. The advance phase of the reach is slowed by occlusion whereas the withdrawal phase of the reach is unaffected (de Bruin et al., 2008; Sacrey & Whishaw, 2012). It is likely that visual and somatosensory attention provide the coordinates for the food item and the mouth respectively, as these are the end-points of each phase of the reach-to-eat movement. For example, visual occlusion of the target disrupts transport and grasping (Hesse & Franz, 2009; Hesse & Franz, 2010; Karl, Sacrey, Doan, & Whishaw, 2012; Winges, Weber, & Santello, 2003) but does not disrupt withdrawal and mouth placement (de Bruin et al., 2008; Sacrey et al., 2012). The tight coupling of the phases of the reach-to-eat movement with visual and

somatosensation respectively, raise the question of when this coupling is acquired in development. This question was addressed in the present study.

Healthy infants were filmed monthly from six months of age to twelve months of age as they reached for familiar targets that they grasped and brought to the mouth. The study was divided into two parts based on reaching targets. Consistent with adult reaching, ten-to-twelve-month-old infants reached for small food items that were grasped and brought to the mouth for eating. To examine reach-to-eat movements at earlier ages, six- to nine-month-old infants reached for small familiar toys that were grasped by the hand(s) and withdrawn to the mouth for oral exploration. Toy targets were chosen to avoid potential choking hazards. A group of healthy adults were filmed as they reached for medium sized toys and small food items to control for any potential differences the two reach targets had on the temporal relationship of arm and eye movements. Hand and eye movements were digitized offline using Peak Motus movement analysis program to determine the duration of visual fixation time for eye movements and the duration of movement time for hand movements, as well as their temporal relationship at each month marker.

Materials and Methods

Subjects

Healthy infants. Nine healthy, full term infants (five boys and four girls) participated in the study. Consistent with the average population of southern Alberta, all infants were Caucasian. The infants in the study were from uncomplicated

deliveries and were healthy, with no known sensory, motor, or neurological impairments. The infants were recruited from acquaintances of an author (LRS). At the beginning of the study, infants were six months of age ($M \pm SD = 6 \text{ months } 0.5 \pm 0.76 \text{ days}$) and at the end of the study, infants were twelve months of age ($M \pm SD = 12 \text{ months } 1.63 \pm 2.26 \text{ days}$). One baby (a male) was excluded from analysis due to incomplete video-recording procedures. Informed consent was obtained from the parent(s) prior to the onset of the study. At the end of the study, the parents were given the Sony miniDV video camera with which they filmed their children to thank them for participating in the study.

Healthy adults. Twenty healthy young adults ($M \pm SD = 20.67 \pm 2.40 \text{ years}$) also participated in the study to determine the adult norm for the reach-to-eat movement. The adults were self-reported to be in good health with no history of neurological disorder, were right handed, and all had normal or corrected to normal vision. The adults were recruited from an undergraduate class at the University of Lethbridge and received course credit for their participation. Informed consent was obtained from subjects prior to the initiation of the testing session. The University of Lethbridge Human Subjects Research Committee approved the study.

Procedure

Infants and adults performed a seated reach-to-eat task in which they reached towards a target that was grasped by the hand and withdrawn to the mouth (de Bruin et al., 2008; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002). Infants were video-

recorded at their place of residence by their parents, monthly from six months of age to twelve months of age. Video recording began as infants turned six months of age because goal directed reaching becomes reliable after six months of age (Bower, 1974; Bruner, 1969) and continued until the infants turned 12 months of age, an age at which infants develop precision grasping (von Hofsten & Fazel-Zandy, 1984). After each filming session, one researcher (LRS) viewed the infant tapes to ensure the parent(s) were following the filming procedures set out in the protocol (see below). The parents were contacted two days prior to the next scheduled video-recording session to remind them to film their child and to remind them to follow the agreed upon video-recording procedures for the age of their child. The infants were filmed for a minimum of ten minutes or a minimum of twenty successful reaches (i.e. grasp and place the target into the mouth).

The experiment was divided into two parts based on the reach target (food and non food), consistent with previous methodology (Berthier & Carrico, 2010). Infants aged ten to twelve months reached for small food items (Cheerios™) to be comparable with adult reach-to-eat literature (de Bruin et al., 2008; Melvin et al., 2005; Sacrey et al., 2011) and because it has been documented that the incidence of “mouthing” non-food items decreases between nine and twelve months of age (McCall, 1974; Ruff, 1984). In order to examine sensory control of reach-to-mouthing behaviour in younger infants, infants aged six to nine months reached for small toys, to avoid a potential choking hazard. Although toys are not a “food item”, young infants systematically bring grasped objects to their mouth for oral exploration (Rochat, 1989; Piaget, 1952). Previous examination of movements made towards both toy and food targets revealed that infants used the same movements when reaching for

small food items and small toys, therefore the use of different reaching targets did not impact reaching strategy (Sacrey et al., 2012).

Filming Instructions

In order to maintain standard video-recording procedures, one researcher (LRS) met with the parents and completed the first video-recording session with the parents to instruct them on how to film their child, which toys/food to use, and how to present the toy/food to the infant to elicit grasping.

The parents were given a set of written instructions, which detailed the procedure, the dates to film their child, what toys/food to use, and how to present the toys/food to the child. The parents had to agree to follow the written procedures to be included in the study. The toy targets reached for by the infants were the infants' own toys, a selection of ten which were chosen by the experimenter. To be included as an "experimental toy", the toy had to fit two criteria: 1) easily graspable by one hand and 2) the width of the object no greater than 7 cm. If, during the filming, the parent had the child reach for an unapproved toy, that toy was excluded from all analyses. Thus, the infants reached for the same set of toys in each of the seven sessions. The parent chose one of the ten toys and presented the toy at arms length, in front (midline) of the infant. Once the infant grasped the toy, the parent loosened their grip so that the infant could withdrawal the toy to the mouth for oral exploration. At ten months of age, the infants then additionally reached for small food items. Parents were instructed to have their child reach for Cheerios™ or Fruit Loops™, food items that

could elicit precision grasping. The seating apparatus was adapted to each of the two grasping targets:



Figure 1. (A) Six-to-nine-month-old infants are seated in a back and neck supportive chair with their hands and arms free to grasp small toys (insert) their parent holds in front of them at the midline and at arms length. (B) Ten- to twelve-month-old infants are seated in a highchair with an attached tray. A food item (insert) is placed at the far end the food tray for the infant to grasp and withdrawal to the mouth. (C) Adults are seated in a chair with their feet flat on the floor. A medium sized toy (insert) is held in front of them at the midline and at arms length. (D) Adults are seated in a chair with their feet flat on the floor. A food item (insert) is placed on a pedestal in front of them to grasp and withdrawal to the mouth.

Reach-to-oral exploration: Six- to nine-months-old infants were seated in a neck and back supportive chair, with the hands and arms free to grasp and manipulate objects, as per previous methodology (Konczak, Borutta, & Dichgans, 1997; Sgandurra et al., 2012), see Figure 1A. The parent held the target toy at an approximate distance of the infants arm's length at the midline of the infants body.

The infant reached towards the toy, grasped the toy with the hand(s), and withdrew the toy to the mouth for oral exploration. The trial ended when the toy was placed into the mouth. Once the target was taken from the mouth, the parent removed the toy and a new toy was offered to initiate a new trial. Target toys were selected depending on the infants' interest and motivation. For example, at six months of age, infants reached for wrist rattles, and at eight months of age, infants reached for small animals. Because the target toys were the infants' personal toys, a familiarization phase was not necessary to habituate the infant to the toy.

Reach-to-eat: Ten- to twelve-months-old infants were seated upright in a high chair with the tray table attached, with the hands and arms free to grasp and manipulate objects, see Figure 1B. A high chair was chosen for the reach-to-eat task to compare with the seated posture of the adults. The parent placed a small food item (e.g., Cheerios™) or small toy on the far end of the high chair tray, at an approximate distance of the extended arm. The infant reached towards the food item/small toy, grasped it with the hand, and withdrew it to the mouth for eating/oral exploration. The trial ended when the food item was released into the mouth and the hand was carried away from the mouth and held in a resting position or the small toy was brought to the mouth for oral exploration. The parent then either placed a new food item on the tray to initiate a new trial or removed the toy from the mouth and placed a new toy on the tray. A previous analysis of reaches completed by the infants compared movement components of reaches made towards toy targets and reaches made towards food targets. These analyses revealed no differences in movement components of reaches made towards the differing targets, apart from grasp shaping (Sacrey et al., 2012). Because the older infants did not always bring a grasped toy to the mouth to orally

explore it and there were no differences in the movement components of the two reach targets, the analyses for ages 10 to 12 months consisted only of completed reaches towards food targets.

Reach-to-oral exploration: Adults were seated in a comfortable upright position, with their feet flat on the floor, see Figure 1C (de Bruin et al., 2008). One experimenter (LRS) held a target toy at an approximate distance of the adults arm's length at the midline of their body. The adult reached towards the toy, grasped the toy with their dominant (right) hand, and withdrew the toy towards the chin. The toys were not placed in the mouth for sanitization reasons because all adults reached for the same set of toys. The trial ended when the hand was resting on the lap while holding the toy steady. Once the target was taken from the adult, the experimenter held a new target toy in front of the participant to initiate a new trial. Target toys were selected based on two criteria: 1) to mimic the type of toys the infants reached for, and 2) be larger than the participants hand to elicit whole hand grasps and control for object-to-hand size ratio in the infant toy condition. The reaching targets for the adults were a hard plastic dinosaur, a wooden spoon (held vertically), a yellow ball, a plushy dog, and a section of train track (held horizontally). Because the target toys were unfamiliar to the participant, three practice trials were given for each toy prior to test trials. During the testing phase, each toy was reached for five times, presented in a pseudo-random order. Each testing trial was initiated with a verbal "ready" signal, immediately followed by a verbal "go" signal as a permissive cue to start the trial at their leisure. The experimenter maintained a casual relationship with the subjects, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition.

Reach-to-eat: Adults were seated in a comfortable upright position, with their feet flat on the floor, see Figure 1D (de Bruin et al., 2008). A self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° extension) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion). The adults were instructed to reach for food with their dominant hand. Each testing trial was initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure. Each trial concluded following successful placement of the food item in the mouth and the return of the reaching hand to its start position on the lap. The experimenter then placed a new food item on the pedestal to initiate a new trial. The experimenter maintained a casual relationship with the subjects, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition.

Sampled Reaches

The first 10 successful reaches per infant, per time point were used in the analysis. A successful reach was defined as reaching towards the target, grasping the target, and withdrawing the target to the mouth for oral exploration/eating (80 reaches for each age measured). An unsuccessful reach was defined as reaching towards and grasping the target without placement of the target into the mouth. Unsuccessful reaches consisted of playing with the target rather than withdrawing it to the mouth

for eating and were infrequent. Eighty reaches were collected for each time point, with a total of 560 reaches included in the analysis. Ten reaches per adult in the toy and food item groups were included in the analysis.

Reach Measurement

Changes to the duration of the reach-to-eat movement, as well as the contribution of visual feedback on the target were measured using kinematic analysis. A digital video camera was positioned in front of the infant or adult to record a frontal view of the participant from lower leg to head for video recording at 30 f/sec, with a shutter speed of 500 frames per second (a high shutter speed produces blur-free images and can capture rapidly occurring movements of the eyes and hands). The trial reaches were digitized using Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the moving points by cursor with an output of 30 Hz. A frame grabber was used to project each frame and manually digitize each chosen biomarker on the image (e.g. ulnar styloid process). The system enhances each of the half-frame (fields) and presents them separately, thus converting 30 frames/second video sequence into 60 frames/second (Field, Whishaw, & Pellis, 1996; Pellis & Pellis, 1994; Whishaw, 1996; Whishaw & Pellis, 1990). For the purposes of this study, duration of movement time was the main objective of the kinematic analysis, not the kinematic measures of velocity or the acceleration of the reaching wrist.

Hand movement. Reaches were digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize

the ulnar styloid process (reach wrist). The data were acquired via a manual mode, digitizing the moving points by cursor. The ulnar styloid process was analyzed to determine movement duration and velocity during the reach-to-eat movement. The events of movement onset and offset were determined from the resultant reach wrist velocity, with minimal resultant velocity used to indicate the onset and offset events for the movement phases of the reach-to-eat movement for each individual trial. Peak Motus allows insertions of visual markers in the data to denote approximate onset and offsets of movement phases (i.e. movement onset, grasp, eat). Specifically, the reach-to-grasp phase (hereafter referred to as *advance*) was defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the target item). The grasp-to-eat phase (hereafter referred to as *withdrawal*) was defined as the time between the second velocity onset (i.e. first movement of hand away from parents hand/tray table) and the subsequent point of minimal velocity (i.e. as the target item contacts the mouth). *The total reach duration* was defined as the time between initial velocity onset (i.e. first movement of the hand) and the second subsequent point of minimal velocity (i.e. as the target item contacts the mouth; de Bruin et al., 2008).

The transport component of the reach was also analyzed as two separate phases, reach (movement onset to first contact) and grasp (first contact to grasp finalization) in accordance with previous methodologies of infant reaching (Konczak et al., 1997; Thelen, Corbetta, & Spencer, 1996). Analyses did not result in any age-related differences for either the transport or grasp phase when separate. The two phases were subsequently combined into “advance” to accord with previous research examining the contributions of visual attention on reach-to-eat behaviour (de Bruin et

al., 2008; Sacrey et al., 2011).

Eye movement. Eye movement was measured using Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO). The data were acquired via a manual mode, digitizing the moving points by cursor. The pupil of the right eye and the right nostril of the nose were tracked from the point when the target entered into the infant's field of view until the target was placed into the mouth with a sampling frequency of 30 Hz. To correct for movement of the head, the velocity of the nostril was subtracted from the velocity of the pupil to calculate a resultant pupil velocity:

$$\text{Resultant Pupil Velocity} = \text{Pupil Velocity} - \text{Nostril Velocity}.$$

The events of eye movement onset and offset were determined from the video record and the resultant pupil velocity (Microsoft Excel 2011). Visual markers were inserted in the data to denote the point at which the infant or adult visually fixated the target and visually disengaged from the target and the exact timing of visual fixation and visual disengagement were determined from the kinematic record. Specifically, eye movement onset (hereafter, *visual fixation*) was defined as the first point of minimal velocity; eye movement offset (hereafter, *visual disengagement*) is defined as the subsequent point of velocity increase; the *total visual engagement duration* was defined as the time between the first point of minimal velocity (i.e. visual fixation) and the subsequent point of velocity increase (i.e. visual disengagement). The contribution of visual feedback for completion of the advance and withdrawal phases of the reach-to-eat movement was calculated using Microsoft Excel (2011).

Specifically, *engage-to-move* was defined as the duration of time between visual fixation and the onset of hand advance. *Grasp-to-disengage* was defined as the duration of time between visual disengagement and grasp of the target (de Bruin et al., 2008).

Onset and Offsets

The onset and offset of the movement phases were identified by the video record as well as the kinematic profiles. Trial onset was defined as an eye movement directed towards the target, or (rarely) the first hand movement towards the target, if occurring before an eye movement towards the target.

Transport, grasp, and eat. The authors (LRS and IQW) analysed the reaching movements of the infants to determine the onset and offset movements of the movement phases for each reach included in the analysis. Movement onset was described as the first frame in which a movement was made towards the target. Grasp was described as the frame before the target was lifted from the substrate. Eat was described as the frame where the lips are closed around the target. The time code for each onset and offset was recorded and a visual marker was inserted into the data using Peak Motus for kinematic confirmation.

Fixation and disengagement. The authors (LRS and IQW) analysed the eye movements of the infants and agreed on “visual fixations” and “visual disengagements” for each trial that was included in the data analysis. Visual fixations and visual disengagements were inferred from gaze direction towards and away from

the target. Visual fixation on the target was defined as an eye movement directed towards the target, with continuous visual fixation of the target as the hand transported towards it and the target was grasped. Visual disengagement was defined as an eye movement away from the target or a blink accompanied with a redirection of gaze away from the target. The time code for each onset and offset was recorded and a visual marker was inserted into the data using Peak Motus for kinematic confirmation. Only those visual fixations on the target that were maintained prior to hand movement onset were included in analysis, however multiple fixations prior to movement onset were rare. To assess the reliability of this method, the temporal coupling of hand and eye movements using biomechanical markers and eye tracking glasses (data presented in de Bruin et al., 2008) was compared to manual tracking of the wrist and eye movements (present paper). Figure 2 compares the resultant temporal coupling of eye and hand movements in healthy adults using frame-by-frame manual tracking using the kinematic analysis program Peak Motus (this study) to the results of temporal coupling of eye and hand movements in healthy adults using a head-mounted infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) and biomechanical markers to track the reaching wrist (previously collected data; de Bruin et al., 2008). It is of note that the coupling of visual fixation to hand movement onset and the coupling of visual disengagement to grasp are equally apparent using both the eye tracking (automatic) and Peak Motus (manual) methods.

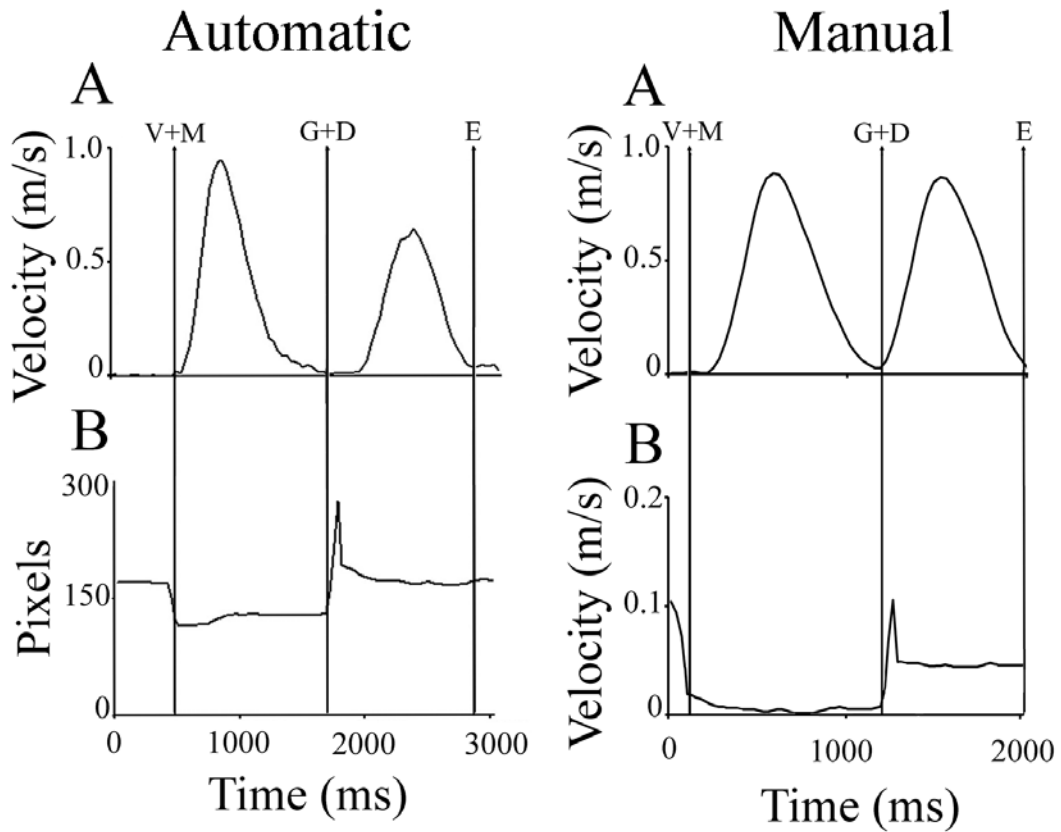


Figure 2. Comparison of the automatic and manual methods for tracking hand and eye movements. Automatic (left panel). (A) Representative velocity profile of the reaching wrist using biomechanical markers. (B) Representative displacement profile of the right pupil using the MobileEye eye-tracker. Manual (right panel). (A) Representative velocity profile of the reaching wrist using manual, frame-by-frame tracking of the ulnar styloid process. (B) Representative velocity profile of the right pupil using manual, frame-by-frame tracking of the moving pupil. Note the temporal coupling of visual attention with hand movement onset and visual disengagement with grasp for the automatic and manual methods. Abbreviations: V – visual fixation; M – hand movement onset; G – grasp; D – visual disengagement; E – eat. Eye-Tracking example adapted from de Bruin et al (2008).

Grasp Shaping

The grasp shaping used by each infant to purchase the target item were collected and compared at each time point. Grasp shapes were measured from all of the reaches collected at six, nine, and twelve months, not just those included in the “reach measurement” analyses. From the grasp shapes collected, three grasping shapes were identified and used in the analysis. The three grasp shapes are described below:

(1) *Whole hand shaping*. Whole hand shaping (Figure 3 A-B) was defined as an open hand with digit open and extended (Figure 3 A). The target is grasped using the whole hand (Figure 3 B).

(2) *Pre-precision shaping*. Pre-precision shaping (Figure 3 C-D) was defined as a closing of the digits with digit flexion present (Figure 3 C). The target is grasped using three or more digits (Figure 3 D).

(3) *Pincer shaping*. Pincer shaping (Figure 3 E-F) was defined as closing and flexion of digits three through five with thumb and digit 2 in an open opposition (Figure 3 E). The target is grasped using the thumb and digit 2 (Figure 3 F).

Each occurrence of grasp shape was recorded for each infant at each time point measured and the proportions of each grasp shape relative to the other recorded grasp shapes (i.e. frequency of one grasp shape/frequency of all three grasp shapes) were calculated for each infant and used in the analyses.

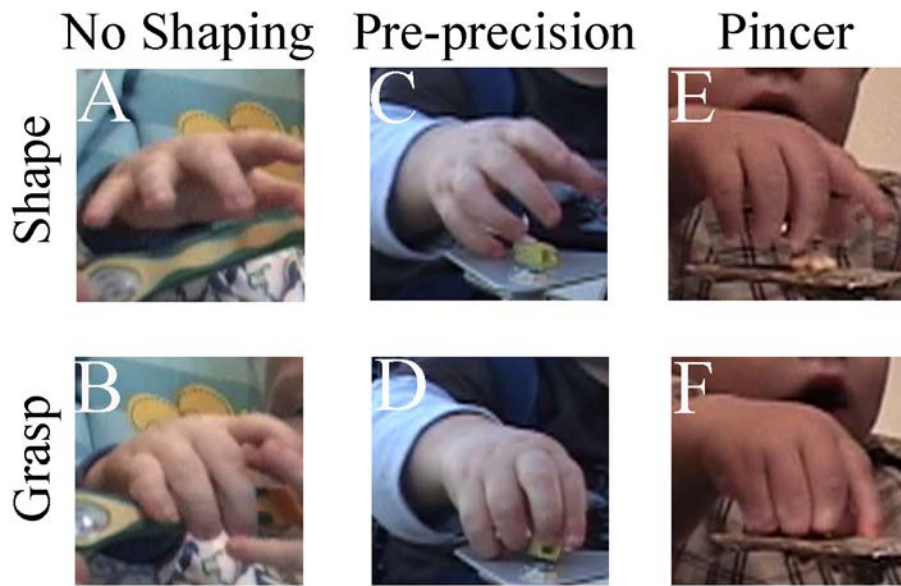


Figure 3. Example photographs of digit shaping and grasps. (A) Whole hand shaping and (B) whole hand grasp. (C) Pre-precision shaping and (D) pre-precision grasp. (E) Pincer shaping and (F) pincer grasp.

Errors

Grasping and mouth placements were analyzed for the presence of errors at six, nine, and twelve months of age. Errors were measured from all of the reaches collected at each six, nine, and twelve months, not just those included in the “reach measurement” analysis.

Grasping errors. Of all grasps completed by the infants, five categories of errors were identified and used in the analysis. The five grasp errors are described below:

(1) *No error*: The target is grasped without error; the digits contact the target and flex and close to grasp the target.

(2) *Undershoot target*: The hand undershoots the location of the target and a second advance is made towards the target.

(3) *Overshoot target*: The hand overshoots the location of the target and the hand withdraws to the location of the target.

(4) *Touch/adjust*: After contact with the target, the hand releases contact and readjusts to re-grasp the target.

(5) *Drop*: Target drops from the infant's hand after it is grasped and removed from the parent's hand/tray.

A subset of all grasps (25%) were scored by two experimenters (LRS; JMK).

Interrater reliability scores for grasping errors were high ($r = 0.80$, $p < 0.001$), thus only the scores of LRS were used in the analysis.

Placement errors. Of all mouth placements completed by the infants, four categories of errors were identified and used in the analysis. The four mouth placement errors are described below:

(1) *No error*: target placed into the mouth without error; the mouth opens and the target is placed between the lips

(2) *Lip*: target first touches lip before being replaced into the mouth

(3) *Near*: target first touches skin immediately surrounding lips before being replaced into the mouth

(4) *Distal*: target first touches area on face distal to the mouth (e.g., chin, cheek, nose) before being replaced into the mouth

A subset of the mouth placements (25%) were scored by two experimenters (LRS; JMK). Interrater reliability scores for mouth placement errors were high ($r = 0.83$, $p < 0.001$), thus only the scores of LRS were used in the analysis.

Statistical Analysis

The first ten successful reaches (i.e. target is grasped and brought to the mouth for oral exploration/eating) per infant per time point were included in the analysis. The Statistical Package for the Social Sciences (SPSS) v. 19 was used to run the repeated measures with an alpha of 0.05 as significant. Bonferroni corrections were used for follow-up comparisons. A comparison of the adult eye movement data showed no significant difference between toy and food targets for engage-to-move and grasp-to-disengage ($ps > 0.05$). Thus, only the adult data for the food target trials are presented.

Results

The infants were always able to successfully advance either their left or their right hand to the target, grasp the target with their hand, to withdraw their hand towards their mouth, and to place the target into their mouth. Nevertheless, the duration of the reaching movement, the contribution of visual attention on the target, grasp pre-shaping, and errors differed depending on the age of the infant. The younger infants were 1) slower to advance their hand towards the target for grasping, 2) visually attended the target for an increased duration of time prior to hand movement onset, 3) continued to visually attend the target for a longer duration of time following the grasp, 4) did not pre-shape their hand in preparation for grasping, and 5) made grasping and mouth placements errors. By twelve months of age, infants 1) visually fixate the target just at hand movement onset, 2) visually disengage from the target as

it is grasped, 3) pre-shaped their hand to grasp the target with a pincer grasp, and 4) made few, if any, grasping and mouth placement errors, as do healthy adults. There was gradual development of the temporal coupling of visual attention to hand advance and grasping and somatosensory attention to hand withdrawal and mouth placement between six months and twelve months of age and is illustrated in Figure 4.

Details of these results will be described in four sections: reach duration, eye movement analysis, grasp shaping, and errors. Reach duration measured the duration of time from movement onset until the target was grasped (*advance*) and from grasp until the target was placed in the mouth (*withdrawal*). Eye movement analysis measured the contribution of visual attention for the reaching movement, specifically the duration of time visually attending the target prior to hand movement onset (*engage-to-move*) and the duration of time visually attending the target after the grasp (*grasp-to-disengage*). Grasp shaping compared each grasp used by the infant to purchase the target, specifically, the use of whole hand grasping, the presence pre-precision grasping, and the use of a pincer grasp. Error analysis measured the accuracy of grasping and mouth placements.

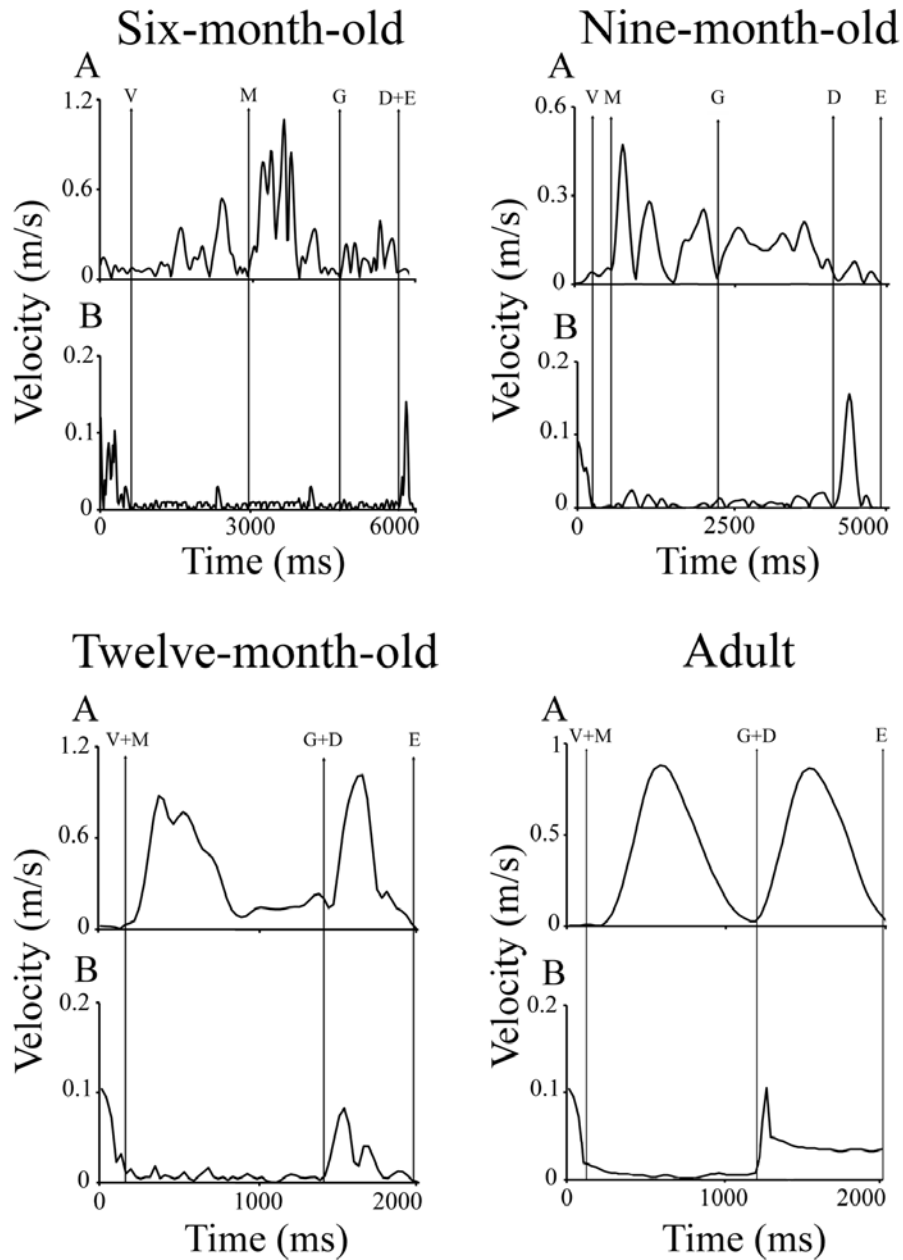


Figure 4. Representative examples of the temporal coupling of (A) hand and (B) eye movements for six- (top left), nine- (top right), and twelve-month-old infants (bottom left), and adults (bottom right). Abbreviations: V – visual fixation; M – hand movement onset; G – grasp; D – visual disengagement; E – eat. Note the similarity in the temporal coupling for twelve-month-old infants and adults.

Hand Movement

A summary of the results of reach duration at each age is shown in Figure 5. With the exception of the earliest time point for which durations were longer than the last time point, there was no difference in the duration of the time to complete the advance (Figure 5 top) or withdrawal (Figure 5 bottom) phases across the ages measured.

Advance. A 7 x 10 ANOVA comparing duration of movement time for advance using Age (6, 7, 8, 9, 10, 11, 12 months) and Trial (1,2,3,4,5,6,7,8,9,10) as the within subjects factors did not result in a significant effect for Age ($F(6,42) = 0.88, p > 0.05$), Trial ($F(9,63) = 0.49, p > 0.05$) or Age x Trial ($F(54, 378) = 0.86, p > 0.05$) interactions. A comparison only of ages 6 months and 12 months resulted in a significant effect for advance ($t(79) = 2.51, p < 0.01$), with six month olds taking longer to complete the movement.

Withdrawal. A 7 x 10 ANOVA comparing duration of movement time for withdrawal using Age (6, 7, 8, 9, 10, 11, 12 months) and Trial (1,2,3,4,5,6,7,8,9,10) as the within subjects factors resulted in a significant effect of Trial ($F(9,63) = 2.20, p < 0.05$), but did not result in a significant effect for Age ($F(6,42) = 1.64, p > 0.05$) or Age x Trial ($F(54, 378) = 1.15, p > 0.05$) interaction. Post hoc comparisons of Trial did not result in any significant effects when the alpha level was corrected. A comparison of withdrawal duration for only ages 6 months and 12 months did not result in a significant effect for withdrawal ($t(79) = 1.47, p > 0.05$).

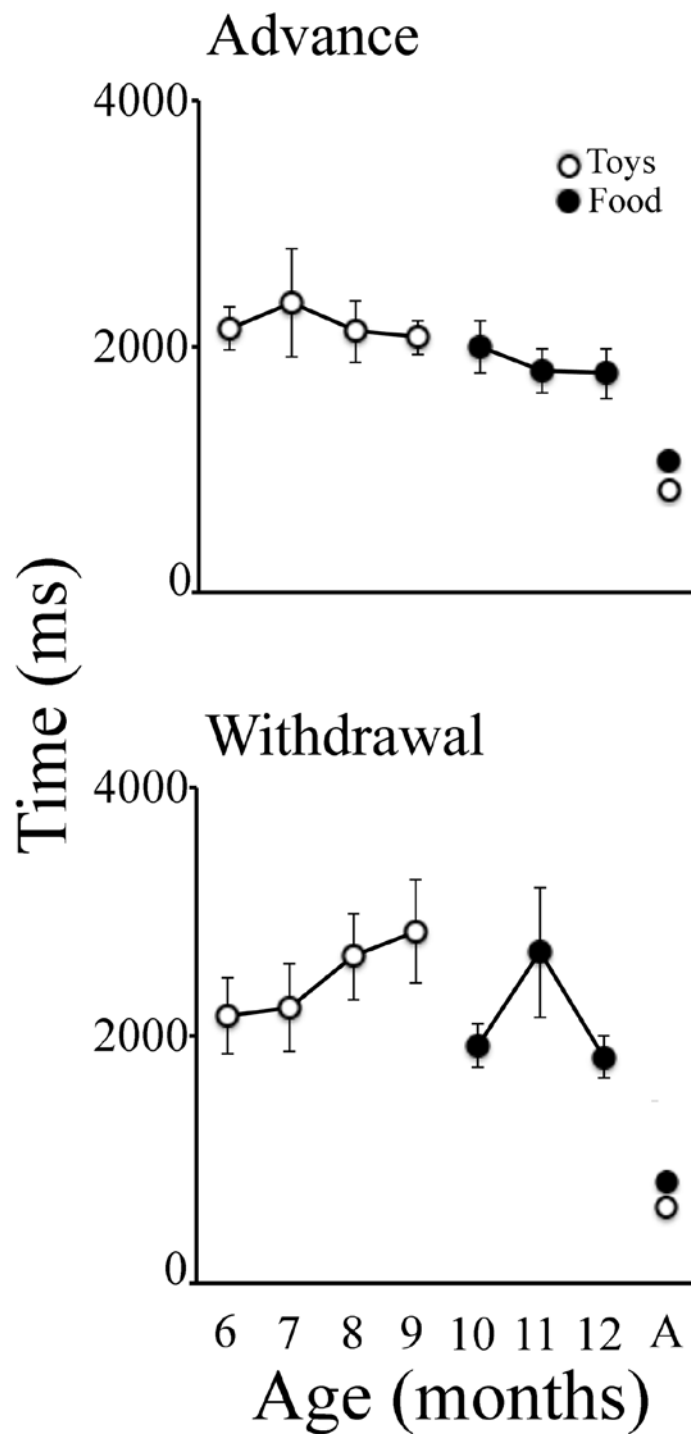


Figure 5. Time (mean $\pm$ standard error in milliseconds) to complete Advance (top) and Withdrawal (bottom) across the seven ages. Adults (A on the x-axis) are included for illustrative purposes. White circles denote “toy” targets and black circles denote “food” targets.

Eye Movement

A summary of the results of eye movement duration for each age is shown in Figure 6. Six-month-old infants had a longer duration of time for looking at the target before hand movement onset (Figure 6 top) and after the target was grasped (Figure 6 bottom) than twelve-month-old infants.

Engage-to-move. A 7 x 10 ANOVA comparing duration of time for engage-to-move using Age (6, 7, 8, 9, 10, 11, 12 months) and Trial (1,2,3,4,5,6,7,8,9,10) as the within subjects factors resulted in a significant effect for Age ($F(2.689,18.823) = 5.81, p < 0.01$), but no significant effects for Trial ($F(3.203,22.418) = 0.64, p > 0.05$), or Age x Trial ($F(5.292,37.043) = 0.73, p > 0.05$) interaction. The data were corrected for sphericity using a Greenhouse-Geisser correction.

Grasp-to-disengage. A 7 x 10 ANOVA comparing duration of time for grasp-to-disengage using Age (6, 7, 8, 9, 10, 11, 12 months) and Trial (1,2,3,4,5,6,7,8,9,10) as the within subjects factors resulted in a significant effect for Age ($F(6,42) = 6.04, p < 0.001$), but no significant effects for Trial ($F(9,63) = 1.24, p > 0.05$), or Age x Trial ($F(54,378) = 0.71, p > 0.05$) interaction.

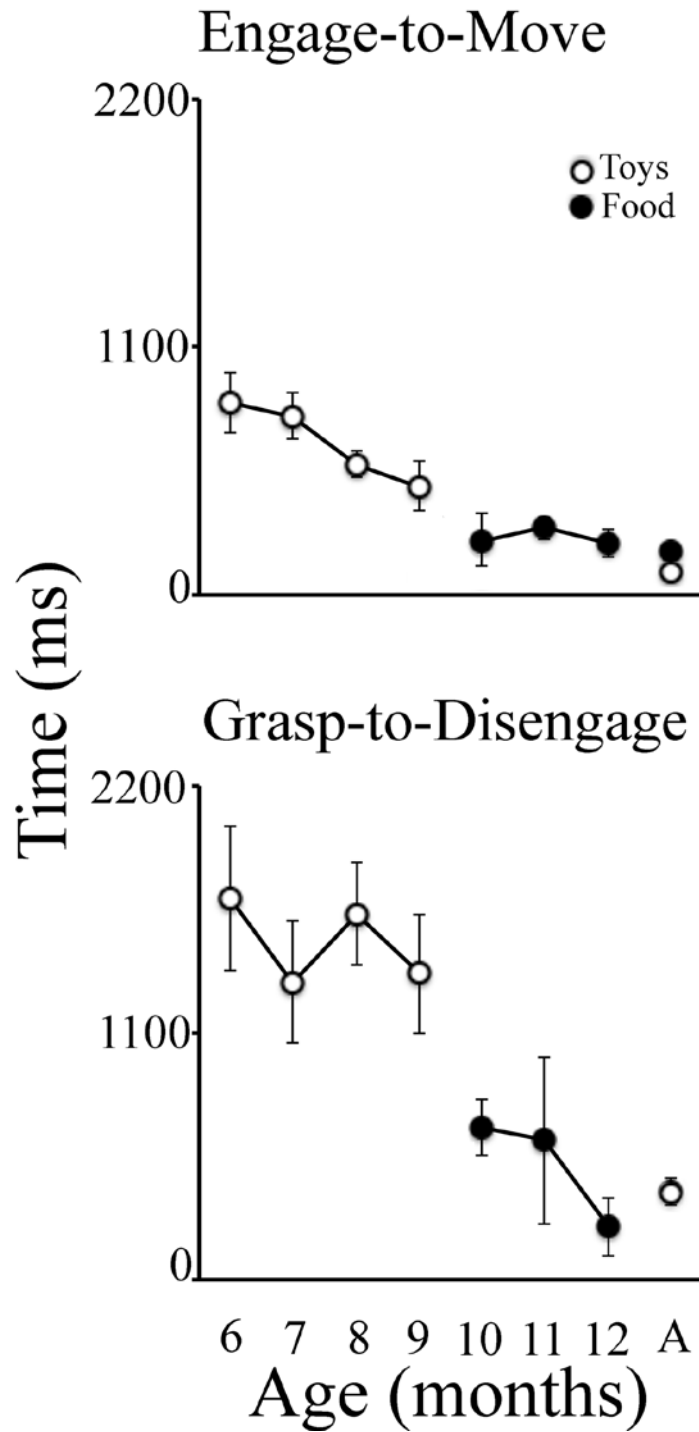


Figure 6. Time (mean $\pm$ standard error in milliseconds) to complete Engage-to-Move (top) and Grasp-to-Disengage (bottom) across the seven ages. Adults (A on the x-axis) are included for illustrative purposes. White circles denote “toy” targets and black circles denote “food” targets.

Twelve-Month Olds versus Adults

A comparison of reach duration and visual attention for twelve-month-old infants and adults is shown in Figure 7. As shown in Figure 7 top, twelve-month-olds (black bars) took longer to complete advance ($p < 0.01$), withdrawal ($p < 0.001$), and total reach duration ($p < 0.001$) than adults (white bars). As shown in Figure 7 bottom, twelve-month-olds (black bars) were comparable to adults (white bars) for engage-to-move ($p > 0.05$) and grasp-to-disengage ($p > 0.05$), but had longer total engagement durations ($p < 0.05$), as might be expected from their longer total reach durations. Thus, by twelve months of age, infants are using vision to guide their movement, as do healthy adults.

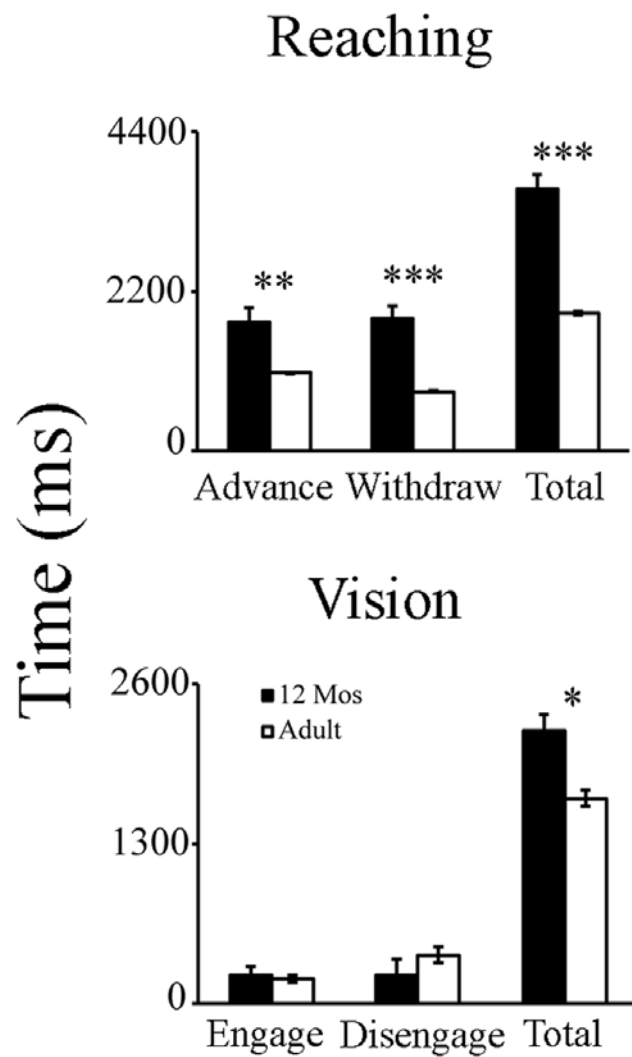


Figure 7. Comparison of time (mean $\pm$ standard error in milliseconds) to complete reaching (top) and visual attention measures (bottom) for twelve-month-old infants (black bars) and adults (white bars) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Grasp Shaping

As displayed in Figure 8, hand shaping gradually matured to reach an adult form by twelve months of age. Six- and seven-month-old infants use whole hand and

digit shaping when preparing to grasp the target and reach towards the target with digits open and extended (i.e. “splayed”). Pre-precision and precision hand and digit shaping appear at eight months of age and increase steadily at each month measured, with pincer grasps comprising 62.03% of all grasp shaping by twelve months of age.

These findings are supported by a 7 X 3 repeated measures ANOVA on grasp pre-shaping using Age (6, 7, 8, 9, 10, 11, 12 months) and Shape (whole hand, pre-precision shaping, pincer shaping) as the within subjects factors. There was no significant effect of Age ($F(6,42) = 1.00, p > 0.05$) or Shaping ($F(2,14) = 3.38, p > 0.05$), but there was a significant Age X Shaping interaction ($F(12,84) = 9.76, p < 0.001$). Follow-up tests showed that six and seven month old infants use whole hand grasping ($ps < 0.001$) and use the pincer grasping more than no shaping at twelve months of age ($p < 0.01$).

Errors

Grasping errors. A summary of the results of grasp errors at six, nine, and twelve months of age are shown in Figure 9. Six-month-old infants make a large number of grasping errors compared to nine and twelve-month-old infants.

These main findings were confirmed by statistical analyses. A 3 x 5 repeated measures ANOVA comparing grasping errors using Age (6, 9, 12 months) and Error (no error, undershoot, overshoot, touch/adjust, drop) as the within subjects factors resulted in a significant effect for Error ($F(4,28) = 155.04, p < 0.001$) and an Age x Error interaction ($F(8,56) = 14.93, p < 0.001$). Follow-up comparisons showed that of

the errors present, six-month-old infants made more touch/adjust errors ($ps < 0.01$) than overshooting, undershooting or dropping the target. Nine-month-old infants made more touch/adjust errors ($p < 0.01$) than overshooting the target. Twelve-month-old infants made more touch/adjust errors ($ps < 0.01$) than overshooting or undershooting the target.

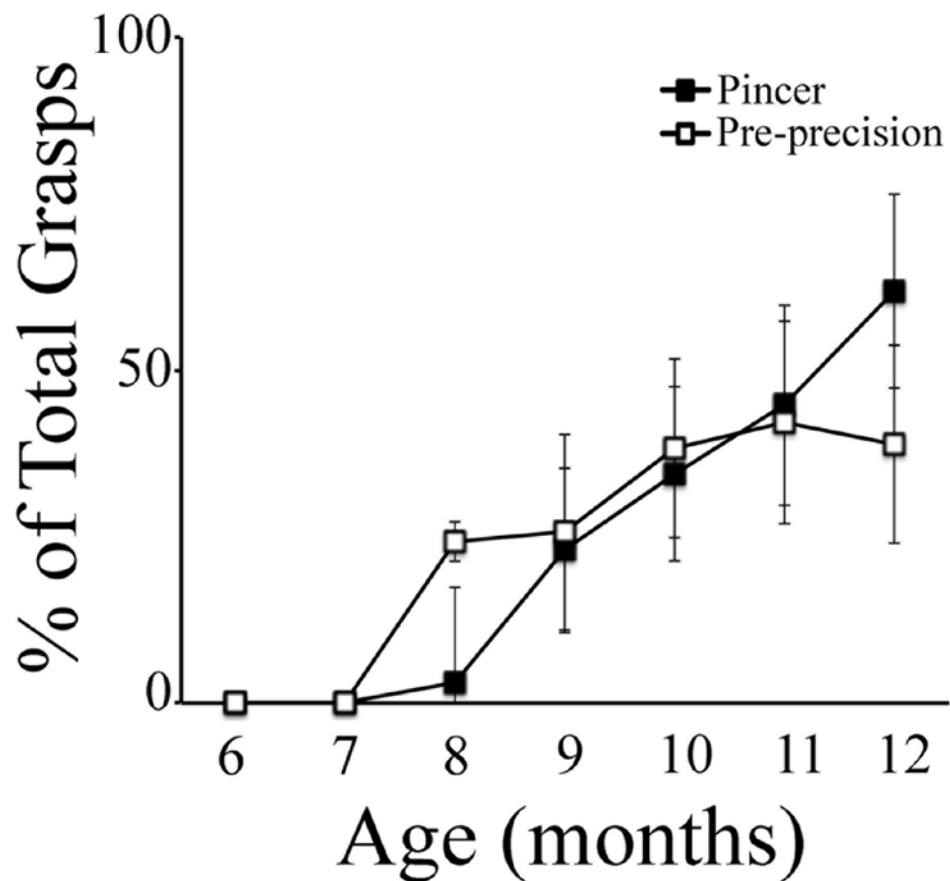


Figure 8. Proportion (mean $\pm$ standard error) of grasp shapes across the seven ages. Note the gradual increased in pre-precision and pincer shaping.

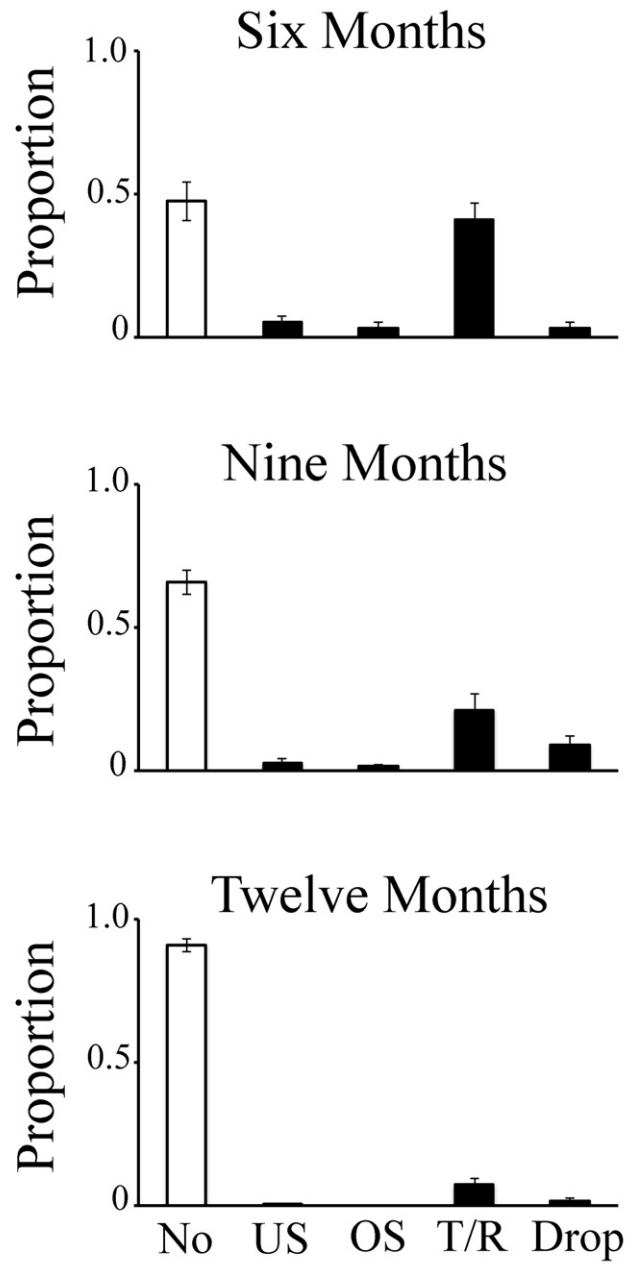


Figure 9. Proportion (mean $\pm$ standard error) of grasp errors at six, nine, and twelve months. Abbreviations: No – no error; US – undershoot; OS – overshoot; T/R – touch and release.

Mouth placement errors. A summary of the results of mouth placement errors at six, nine, and twelve months of age are shown in Figure 10. Six-month-old infants made a larger number of placement errors than nine and twelve month old infants.

These main findings were confirmed by statistical analyses. A 3 x 4 repeated measures ANOVA comparing mouth placement errors using Age (6, 9, 12 months) and Error (no error, lips, near, distal) as the within subjects factors resulted in a significant effect for Error ($F(3,21) = 68.05, p < 0.001$) and an Age x Error interaction ($F(6,42) = 44.58, p < 0.001$). Follow-up comparisons showed that of the errors present, six-month-old infants made more near errors ($ps < 0.01$) than lips or distal errors. Nine-month-old infants made more lip errors ($p < 0.01$) than near or distal errors. Twelve-month-old infants made few errors and showed no error preference ($ps > 0.05$).

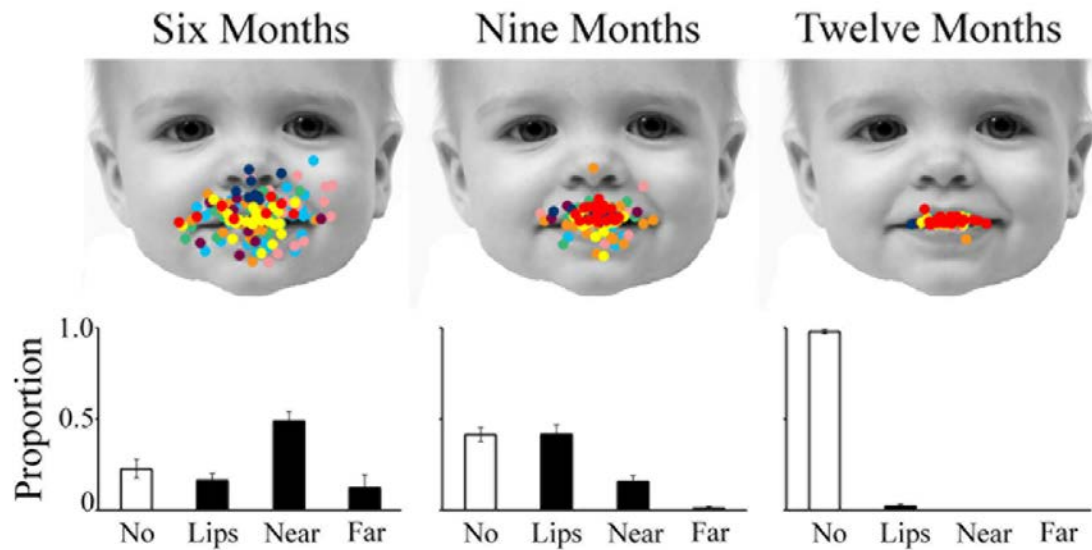


Figure 10. Top. First contacts at six, nine, and twelve months of age. Each dot represents a single touch. Each colour represents a single infant. Bottom. Proportion (mean $\pm$ standard error) of mouth placement errors at six, nine, and twelve months. Abbreviations: No – no error; Lips – touches lips; Near – touch skin surrounding lips; Far – touching skin distal to mouth.

Discussion

This study provides the first description of the development of visual and somatosensory attention for the reach-to-eat movement in healthy infants. Infants were video-recorded at their homes from six months of age to twelve months of age as they reached for familiar toys and food items that they grasped and brought to the mouth. Kinematic measures of movement durations of eye and hand movements were manually derived from the video record. Over the six-month developmental period, the improvement in the reach-to-eat movement toward adult levels was associated with a large variance, suggesting a concomitant development of a number of aspects of reaching performance. These include vision becoming coupled to hand advance

and somatosensation becoming coupled to hand withdrawal, hand shaping changing from a whole hand grasp to a pincer grasp to purchase the target item, and improvement in the accuracy of grasping the target and bringing the target to the mouth. Taken together, these findings show that the temporal coupling of visual attention to hand advance and hand shaping and somatosensory attention to hand withdrawal and targeting the mouth are important aspects of the development of the reach-to-eat movement.

The objective of the present study was to examine the contributions of visual and somatosensory attention to the naturalistic movement, reaching to eat, in infants from six months to one year of age. The study was characterized by three features: 1) testing infants in a home environment, 2) using familiar target objects for reaching, and 3) offline analysis of the video records. Infants were repeatedly tested in a home setting by their parents to decrease testing stress and to ensure the ethological relevance of the task. Familiar toys were selected as reaching targets depending on the infants' interest and motivation. That is, younger infants reached for small wrist rattles and older infants reached for small plastic animals, in addition to small food items. Because the target toys were the infants' personal toys, a familiarization phase was not necessary to habituate the infant to the toy. In addition, it was thought that familiarization would reduce distractions related to examining and manipulating unfamiliar objects. Because the infants were filmed at home, eye and hand movements were measured off-line using manual tracking of the right pupil and the wrist of the reaching hand. The off-line, manual-tracking method was chosen because movement-tracking software that relies on light emitting diodes (LED) or infrared emitting diodes (IRED) is difficult in young infants, especially in a home setting. That

is, the LEDs or IREDs may become occluded or directed away from the camera because the infant cannot be instructed to keep the hand in a single plane (Berthier & Keen, 2006), the infant may repeatedly start and stop a movement, and movement time can vary between infants and trials, making data capture difficult (von Hofsten & Ronnqvist, 1988). Moreover, IRED and LED systems require the application of diodes to the hand that infants may try to remove with their hand or mouth, and which may also result in the infant being distracted and/or reluctant to use that hand because of the attached diodes. The comparability and accuracy of automatic (biomechanical) and manual (frame-by-frame) tracking of arm and eye movements (see Figure 2) was confirmed in healthy adults.

Adults visually fixate the target immediately prior to hand movement onset and disengage the target as the digits are grasping it, as has been described in previous studies (see introduction). In contrast, at the earliest ages, infants spent a comparatively long time visually fixating on the target prior to hand movement onset and following a grasp. By twelve months of age, however, infants were displaying a more adult-like pattern of visually fixating the target immediately prior to hand movement onset and visually disengaging the target as the digits grasped it. Thus, visual attention develops from exaggerated visual attention before and after grasping to the tight coupling of visual attention to hand advance. An important feature of the present study is that visual fixation was exaggerated despite the use of familiar toys and food items that were designed to reduce target exploration. That infants displayed exaggerated visual attention was not surprising because a number of previous studies have noted the exaggerated visual fixation displayed by infants both before moving the hand towards a target and after the target has been contacted by the hand (Bower,

1974; Brunner & Koslowski, 1972; Bushnell, 1985; McCarty et al., 2001; Ruff, 1986). The use of online visual attention to guide reaching and grasping develops by 1 year of age, as infants are successful in grasping the target using a pincer grasp without error.

The developing restriction of visual attention to the advance phase of the reach concomitantly suggests that somatosensory attention for hand withdrawal was maturing in parallel to visual attention. This is an interesting and unexpended finding, given that infants have ample practice bringing their hand to their face and mouth beginning in utero and continuing after birth (Butterworth & Hopkins, 1988; de Vries et al., 2001; Hepper et al., 1991; Hopkins et al., 1988; Piaget, 1952; Sparling et al., 1999). At these early ages, however infants bring only their hand to their face and mouth, but in the present study, infants are bringing a grasped object to the mouth. The addition of a grasped object may require the infant to form a new visual-proprioceptive map for grasped objects, to account for the various intrinsic and extrinsic properties of the item (e.g. weight, size, wrist orientation needed to place target into mouth, etc), similar to how infants form a visual-proprioceptive map for distal reaching (Bushnell, 1985; Piaget, 1952). This “re- mapping” develops by 1 year of age, as infants are successful in bringing grasped objects to the mouth without error.

A striking feature of performance of the infants was the high degree of variance in performance, which even at twelve-months of age exceeded that of the adult subjects. It is unlikely that this variance is accounted for solely by an increase in time that the infants spent examining the target at the earliest ages because the use of

familiar toys and food items was intended to reduce this behaviour. The variance is likely, in part, related to the development of other aspects of performance that need to be integrated with visual attention. First, the development of sensory attention was likely associated with increased accuracy in targeting the object with the hand and the mouth with the object. Adults do not show errors in grasping a target or placing a target into the mouth (de Bruin et al., 2008). At the earlier ages the infants made many errors in both grasping the target and in directing the target into the mouth. Second, the development of sensory attention might also be related to the proximodistal development of reaching, in which more proximal control of arm advance predates more distal hand shaping for grasping (Armand, Olivier, Edgley, & Lemon, 1997; Berthier et al., 1999; Kuypers, 1981; Olivier, Edgley, Armand, & Lemon, 1997; White et al., 1964). Third, the development of sensory attention might also depend upon the development of more adult-like hand shaping as infants progressed from using a whole hand grasp at six months of age to developing precision grasps by at about ten months of age (Touwen, 1976; von Hofsten & Fazel-Zandy, 1984; White et al., 1964). The use of whole hand grasps in the earliest time points may have been in part a product of the larger items (small toys) requiring a whole hand grasp but more likely maturation of the neuromuscular system contributed.

Taken together, therefore, the results of the study suggest that sensory attention, movement skill, and movement accuracy develop together over ages six months to twelve months. Substantial work has emphasized the role of development of the corticospinal system in precision grasping (Courtine et al., 2007; Lemon, 2008) but the present study emphasizes that the development of sensory attention for guidance of hand movements is an equally important developmental feature of reach-to-eat

movement. In this respect, it is interesting that infants that are as young as four months of age can perform a wide range of precision grip movements (Wallace & Whishaw, 2003) but as is described here, visual and somatosensory guidance of those movements to a distal target and to the mouth is a much later development. The present results suggests that the understanding of precision grasping must be viewed within a framework that includes body and limb movements and the sensory control of these movements both for reaching to targets in space and withdrawing objects to the mouth (Graziano, 2006; Graziano, Aflalo, & Cooke, 2005). As a final comment, it must be noted that even by twelve months of age, infant performance was not quite at adult levels, suggesting there are features of the of infant performance that are not fully mature by this age.

In conclusion, this longitudinal study of the reach-to-eat movement, using frame-by-frame manual kinematic analysis of eye and wrist movements to measure movement duration and the temporal relationship between eye and hand movement, shows that development of the sensory control of reaching develops in concert with other performance aspects of the movement. Thus, over the developmental age examined, there is ample room for learning and integrating neuromuscular and sensory control (Eyre, Miller, Clowry, Conway, & Watts, 2000; Kuypers 1981; Martin, Choy, Pullman, & Meng, 2004; Yakovlev & Lecours, 1967). By twelve months of age, infants are approaching a behaviour that resembles the mature online unconscious reaching described for the dorsal stream (Goodale & Milner, 1992).

Finally, that there is a development of the temporal coupling of vision to hand advance and digit pre-shaping and somatosensation to hand withdrawal and mouth placement may be relevant as an early detection marker in children at risk for

developing neurodevelopmental disorders (Coluccini, Maini, Martelloni, Sgandurra, & Cioni, 2007; Zwaigenbaum, Bryson, Rogers, Roberts, Brian, & Szatmari, 2005).

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Chapter 4

Drug treatment and familiar music aids an attention shift from vision to somatosensation in Parkinson's disease on the reach-to-eat task.

Abstract

Sensory control of reaching for a food target to eat (reach-to-eat) is closely coupled to the successive phases of the movement. Control subjects visually fixate the target from hand movement onset to the point that the digits contact the food, at which point they look away. This relationship between sensory attention and limb movement suggests that whereas limb advance is under visual attention, grasping, limb withdrawal, and releasing the food to the mouth is guided by somatosensory attention. The pattern of sensory attention is altered in Parkinson's disease (PD). PD subjects may visually fixate the target for longer durations prior to movement initiation, during the grasp, and during the initial portion of hand withdrawal, suggesting that vision compensates for a somatosensory impairment. Because both medication and listening to favorite musical pieces have been reported to normalize some movements in subjects with PD, the present study compared the effect of medication and listening to preferred musical pieces on sensory attention shifts from vision to somatosensation during the reach-to-eat movement. Biometric measures of eye movement and the reaching limb were collected from PD subjects and aged-matched control subjects in four conditions in their own homes: off medication, off medication with music, on medication, and on medication with music. Unmedicated PD subjects were slower to visually disengage the target after grasping it. Their disengage latency was shortened by both music and medication. Medication and music did not improve other aspects of reaching, including reaching duration and the ratings of the movement elements of limb advance, grasping, and limb withdrawal. The results are discussed in relation to the idea that one way in which medication and music may aid movement in PD by

normalizing somatosensory attention of forelimb movement thus reducing compensatory visual monitoring.

Skilled reaching, or reach-to-eat, is a natural movement in which a hand is used to grasp a food item and place it in the mouth for eating. Because the movement is present in rodents, nonhuman primates, and humans, it routinely serves as a laboratory model to investigate a variety of neurological conditions, including stroke (Foroud & Whishaw, 2006; Gharbawie, Karl, & Whishaw, 2007), spinal cord injury (Girgis, Merrett, Kirkland, Metz, Verge, & Fouad, 2007; Whishaw & Metz, 2002), and degenerative disorders such as Huntington's disease and Parkinson's disease (PD) (Doan, Melvin, Whishaw, & Suchowersky, 2008; Döbrössy & Dunnett, 2006; Karl, Sacrey, McDonald, & Whishaw, 2008; Melvin, 2005; Vergara-Aragon, Gonzalez, & Whishaw, 2003). Sensory monitoring of the reach-to-eat movement in human subjects is distinctive in that it is closely coupled to the phases of the movement. Control subjects visually fixate the target with a quick eye saccade just before the limb initiates the advance movement to the food and then disengages the target with an eye blink and an alteration in gaze just at the point that the digits contact the food. The coupling of visual attention to limb advance suggests that, whereas limb advance is under visual attention, grasping, limb withdrawal, and releasing the food into the mouth is guided by somatosensory attention (de Bruin, Sacrey, Doan, Brown, & Whishaw, 2008). The relation of sensory attention to the phases of the reach-to-eat movement makes the task useful for investigating the shifts in sensory attention (i.e., visual and somatosensory) of movement in neurological disease such as PD.

PD is caused by the progressive degeneration of dopamine producing neurons in the substantia nigra pars compacta (Dauer & Przedborski, 2003) and is characterized by motor, sensory, and attention impairment (Martinez & Utterback, 1973; Sacks, 1982). In addition, Lewy body inclusions have been noted in the temporal cortex of confirmed stage III PD patients as assessed by Braak Classification (Braak, Del Tredici, Rub, de Vos, & Jansen Steur, 2003), suggesting widespread neural changes in the disease. Forelimb movement impairments have been described in both laboratory-based tasks (Dunnewold, Jacobi, & van Hilten, 1997; Ponsen, Daffertshofer, Wolters, Beek, & Berendse, 2008) and real-world tasks (Castiello, Bennett, Bonfiglioli, & Peppard, 2000; Doan, Whishaw, Pellis, Suchowersky, & Brown, 2006; Tresilian, Stelmach, & Adler, 1997). They are often accompanied by sensory impairments (Baroni, Benvenuti, Fantini, Pantaleo, & Urbani, 1984; Flowers, 1976; Keijsers, Admiraal, Cools, Bloem, & Gielen, 2005; Klockgether & Dichgans, 1994) and if sensory cueing is provided to PD subjects, motor performance can improve (Caird, 1991; Chuma, 2007; Lehman, Toole, Lofald, & Hirsch, 2005; Thaut, McIntosh, Rice, Miller, Rathbun, & Braul, 1996). To illustrate, illumination of the finger improves performance on memory guided pointing (Adamovich, Berkinblit, Henning, Sage, & Pionzer, 2001) in much the same way that auditory (i.e. verbal instructions) or visual (i.e. lines on floor) cueing can improve cadence, stride length and velocity of gait for PD subjects (Bagley, Kelly, Tunnicliffe, Turnbull, & Walker, 1991; Lehman et al., 2005). In addition, reducing visual monitoring of the hand results in greater hand shaping abnormalities (Schettino, Adamovich, Henning, Tunik, Sage, & Pionzer, 2006). Both dopaminergic medication and music can ameliorate PD symptoms (Doan et al., 2006; Mongeon, Blanchet, & Messier, 2009; Pacchetti, Mancini, Aglieri, Fundaro, Martignoni, & Nappi, 2000; Sacks, 1982; Sacrey, Clark, &

Whishaw, 2009; Stern, Lander, & Lees, 1980; Swallow, 1990; Thaut et al., 1996), but the extent to which the treatments act on movement vs sensory attention is unclear.

The findings that medication and music can have a beneficial effect on movement and its sensory attention in PD is interesting and raises the question of whether these treatments might affect sensory monitoring and sensory shifts in the reach-to-eat task. Previous work suggests that, whereas control subjects visually engage a food item in the reach-to-eat task just as they initiate the reach movement and visually disengage the target immediately upon grasping the target (de Bruin et al., 2008), PD subjects fixate the target for a longer duration both prior to reach initiation and following grasping (Melvin et al., 2005; Sacrey et al., 2009). The purpose of the present chapter was to examine whether an alteration in sensory shifting from vision to somatosensation occurs in unmedicated PD patients and to determine whether medication and the effects of familiar music on sensory attention shifting. Age-matched controls (OAC), and adults with PD performed the reach-to-eat task. Eye movements were monitored with an eye-tracking system and hand movements were monitored by video recording and analyzed with kinematic tracking. PD subjects were tested under four conditions in their own homes: off medication, off medication with familiar music, on medication, and on medication with familiar music, and were compared to age-matched controls. Synchronized data from the ulnar styloid process (reach wrist) and the eye-tracking system were compiled to determine the extent of visual attention to the reach-to-eat movement and the effects of familiar music and/or drug treatment on sensory attention of the movement. In addition, movement components of the reach-to-eat movement were examined using a

previously standardized rating scale (Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002).

Materials and Methods

Subjects

PD subjects were recruited from the Parkinson's Society of Southern Alberta (PSSA) city of Lethbridge, Alberta chapter (6 males and 2 females; ages 70.3 ± 6.8 years; Hoehn and Yahr "OFF" mean = 2.0). Individuals were diagnosed with Parkinson's disease by a neurologist with expertise in movement disorders at a local Parkinson's disease clinic (in Raymond, Alberta). PD subjects were all receiving dopaminergic medications as PD treatment, and were tested in both off (> 12 hours removed from last oral drug dose (as per previously described methodology (Joti, Kulashkekhar, Behari, & Murthy, 2007; O'Suilleabhain, Bullard, & Dewey, 2001; Rickards & Cody, 1997); UPDRS motor subset off 32.9 ± 12.9) and on (testing commenced 1.5 hours following oral administration of PD medication; UPDRS motor subset on 24.1 ± 10.2) medications. Testing in the "ON" condition occurred 1.5 hours following oral administration of PD medications for two reasons. The plasma half-life of levodopa occurs 1-3 hours following oral dosing (Goudreau & Ahlskog, 2005) and PD subjects self-reported that they felt their medication was working 1.5 to 2 hours following administration (see Figure 1 for the methodological timeline). Testing in both conditions occurred on the same day at the subjects' place of residence, with testing in the off condition occurring in the morning and testing in the on condition

occurring in the afternoon. The design of the experiment allowed the study to be conducted on a single day for each subject, thus reducing testing stress associated with multiple test sessions. Clinical assessment on the basis of the UPDRS III motor subset confirmed the quality of the on condition (paired t for on versus off medication: $p = 0.001$). For PD subject characteristics, see Table 1.

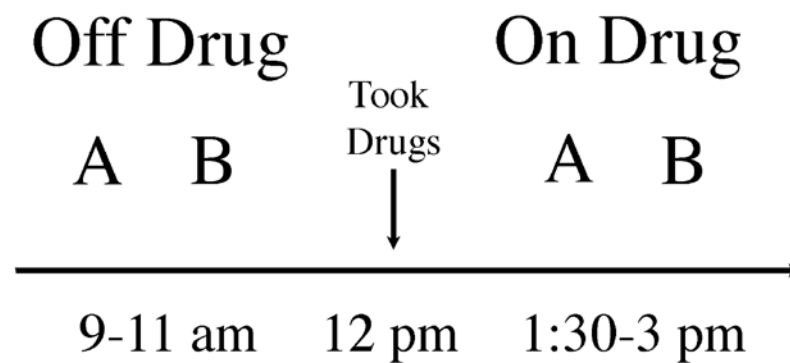


Figure 1. Procedural timeline for the Parkinson's disease subjects. Testing in the off condition began at 9:00 A.M., medication was administered at 12:00 P.M., and testing in the on condition began at 1:30 P.M. A – testing off music; B – testing on music

Table 1.
Parkinson's diseased subjects characteristics

ID	Age	Sex	Hoehn & Yahr	UPDRS III		Medications
				ON	OFF	
JD	72	M	1.5	18	22	Sinemet; Mirapex
ES	77	M	3	31	36	Sinemet
RM	75	M	1.5	20	29	Sinemet
SC	76	F	2	23	38	Carbidopa
DV	67	M	1.5	16	25	Sinemet
LV	68	F	3	44	56	Sinemet
DN	56	M	1	12	15	Sinemet
LVau	71	M	2.5	29	42	Sinemet
Average	70.25	2 F: 6 M	2	24.125	32.875	

Age-matched old adult control (OAC) subjects were recruited from the city of Lethbridge through newspaper advertisement (3 males and 5 females; ages 69 ± 5.78 years). There was no significant age difference between the two groups ($p = 0.70$). All control subjects were self-reported to be in good health with no history of neurological disorder, and all subjects had normal or corrected to normal (contact lens) vision. The University of Lethbridge Human Subject Research Committee approved the study. Informed consent was obtained from subjects prior to initiation of the testing session. The study was conducted in accordance with the Declaration of Helsinki.

Reaching Task

Subjects performed a seated reach-to-eat task in which they reached toward a pedestal for a small food item that was grasped and withdrawn to the mouth for eating (de Bruin et al., 2008; Melvin et al., 2005; Whishaw et al., 2002). Subjects were seated in a comfortable upright position, with their feet flat on the floor (Figure 2). A self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° extension) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion).

Reaching Instructions

Once subjects were seated, they were asked to place their hands palm down on their thighs, and this instruction was not repeated. The experimenter stood to the left of the subject (i.e. in peripheral visual space) and placed a food item (Cheerio™) on the pedestal for each trial. The subjects were instructed to reach for food with their dominant hand. Each testing trial was initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure. Each trial concluded following successful placement of the food item in the mouth and the return of the reaching hand to its start position on the lap. The experimenter maintained a casual relationship with the subjects, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition. Because subjects were not informed that their eye movements were under investigation, they were not asked to fixate on an object in the environment prior to trial initiation.

Reach Measurement

The reach-to-eat movement was measured using kinematic measurement, eye-tracking glasses (de Bruin et al., 2008) and a movement component rating scale (Melvin et al., 2005; Whishaw et al., 2002).

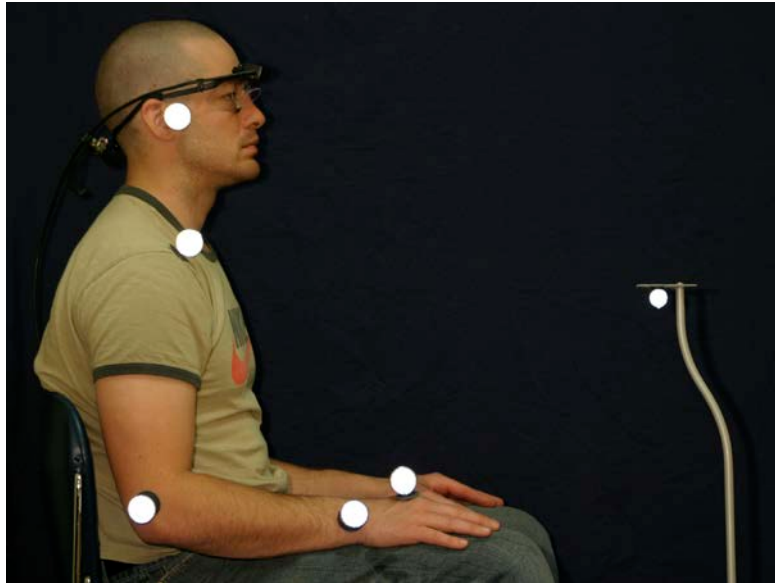


Figure 2. A subject sits before a pedestal on which a food item is placed. Food is placed on the pedestal and the subject begins the first reach with hand open on the lap. The white dots represent light reflective markers on the subject (left) and the food target (right). The headset is for eye-tracking.

Reach duration. A digital video camera was positioned sagittal to the subject to record a reach-side view of the subject from lower leg to head at a sampling frequency of 30 Hz. Trial reaches were digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the ulnar styloid process (reach wrist). The data were acquired via a manual mode, digitizing the moving points by cursor. The ulnar styloid process was analyzed to determine movement duration and velocity during the different phases of the reach-to-eat movement. The events of movement onset and offset were determined from the resultant reach wrist velocity using a custom-written algorithm (Microsoft Excel 2002), with minimal resultant velocity used to indicate the onset and offset events for the movement phases of the reach-to-eat movement. Specifically, the reach-to-grasp

phase (hereafter referred to as *advance*) is defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the food item). The grasp-to-eat phase (hereafter referred to as *withdrawal*) is defined as the time between the second velocity onset (i.e. first movement of hand away from pedestal) and the subsequent point of minimal velocity (i.e. as the food item contacts the mouth). *The total reach duration* is defined as the time between initial velocity onset (i.e. first movement of the hand) and the second subsequent point of minimal velocity (i.e. as the food item contacts the mouth), see Figure 3.

Eye movement latency. Subjects wore a head-mounted infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) to track eye movements with a sampling frequency of 30 Hz (de Bruin et al., 2008). The MobileEye system uses Dark Pupil Tracking to compute the x and y coordinates of the pupil within the scene. In this technique, a set of three harmless near infrared lights are projected onto the eye, and reflected by the cornea (corneal reflection). By comparing the relative vectors from the sensor to the pupil and the cornea, the eye tracking system computes the position of the eye (point of gaze) relative to the scene. The video record of the data collected by the eye tracking system were subjected to off-line analysis to determine the following events of visual guidance: engage-to-move, grasp-to-disengage, and total engagement period. *Engage-to-move* is defined as the time between the first point that the eyes descend to visually fixate the food item and first movement of the forelimb towards the food item, and *grasp-to-disengage* is defined as the time between contact of the food item with the digits and the first point that the eyes disengage from the food item. *The total visual engagement period* is

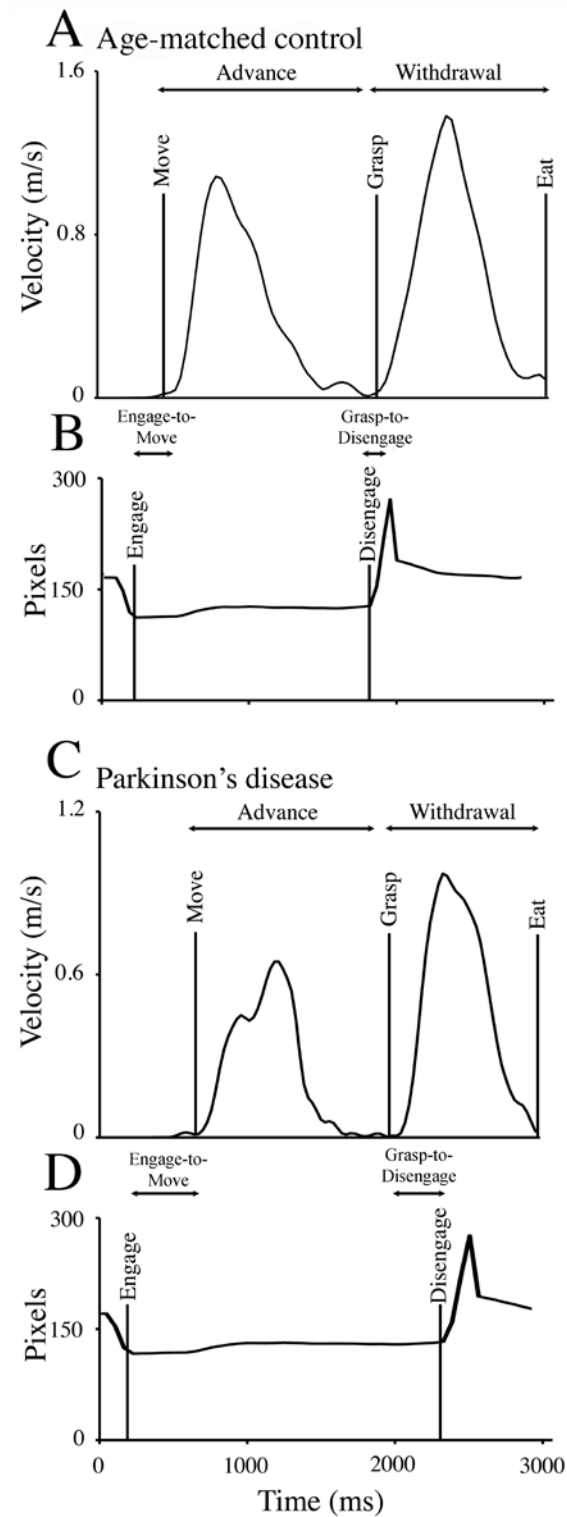


Figure 3. Kinematic measurement of the wrist (A) and eye (B) from an age-matched control and kinematic measurement of the wrist (C) and eye (D) from an unmedicated Parkinson's disease subject during a representative reach. Wrist measurement is measured in velocity (meters/second); eye measurement is measured in location (pixels). Note that eye movement coincides with the advance movement for age-matched controls but the eye continues to fixate the target during the withdrawal movement for Parkinson disease subjects.

defined as the time between the first point that the eyes descend to fixate the food item (*engage*) and the first point that the eyes ascend (*disengage*) from the food item (see Figure 3). A visual marker presented at the onset of the testing session was used to time-synchronize the video record of the reach wrist obtained from the digital camera and the video record from the eye-tracking system offline using Final Cut Pro HD v.4.5 for Mac OS X v.10.2.8.

Movement scoring. Reach trials were scored according to a previously standardized reach-to-eat movement scale that is based upon a movement notation analysis of the reaching movement (Whishaw et al., 2002) to confirm that the sample population in the present study is representative of healthy and PD populations. A reach trial from each of the four conditions (no treatment, music only, drug only, and music and drug) for Parkinson subjects and one reach trial for both conditions (no music and music) for age-matched controls were scored to compare the different treatment subgroups with the no treatment control. The scored reaches were the first successful test reach of the no music and music conditions for age-matched controls and no treatment, music only, drug only, and music and drug conditions for PD subjects, as per methodology used in previous papers (Melvin, 2005; Melvin et al., 2005; Sacrey et al., 2009; Whishaw et al., 2002). The scale is an extension of a traditional method of movement analysis (Eshkol & Wachman, 1958), consisting of 21 items combined into eight temporally sequenced elements. For each of the eight elements, a score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent (for a full description, see Melvin et al., 2005; Whishaw et al., 2002).

Familiar Music

Prior to initiation of the testing session, subjects were asked to select two songs from their favorite artist. The self-selected music was played on a personal listening device (iPod, Apple, Cupertino, CA) during reaching in the music condition. The music was not embedded with rhythmic auditory stimulation (RAS).

Procedure

Subjects with PD were filmed in two sessions, both off and on their medications. For the off condition, PD subjects were asked to abstain from taking their medications after 6:00 PM the night before filming until they were filmed in the off condition. Filming for the off condition occurred between 9:00 A.M. and 11:00 A.M., ensuring PD subjects were off medication for at least 12-hours. Following completion of filming, PD subjects were asked to take their medications with lunch (at 12:00 P.M.). Filming in the on condition occurred between 1:30 P.M. and 3:00 P.M. Age-matched controls were filmed in one session. All subjects were filmed at their place of residence.

For each filming session, subjects were given the opportunity to reach for a maximum of three practice trials of the reaching task without music in order to allow the subjects to become familiar and relaxed when performing the task. Following the practice trials, subjects completed three trials of the reaching task without music followed by three trials of the reaching task with music. Thus, each testing session consisted of three practice trials followed by three test trials without music and three

test trials with music. Three reaching trials per condition were chosen to ensure that PD subjects would be able to complete the task before getting fatigued. The order of trials (i.e., no music followed by music reaches) was chosen to avoid any potential carry-over effects of music on non-music reaches.

Statistical Analysis

Data were analyzed using repeated measures ANOVA (Statistical Package for the Social Sciences, SPSS v. 16). Bonferroni correction for post-hoc tests was used for all pairwise comparisons. Post hoc were limited to comparing the treatment conditions to the no treatment condition.

Results

Age-Matched Controls

Reach duration and eye movement latency. A summary of the results of eye movement latency and the reach duration of the aged-matched controls in both the music and no music conditions is shown in Figure 4. The age-matched control subjects fixated the target just before they initiated the reach and disengaged from the target just as the fingers grasped it. There was no difference between the music and no music condition for latency of the eye to fixate the target or to disengage from the target. Similarly, there was no difference in the duration of the advance or the withdrawal movement of the limb in the no music and music conditions.

These main finding were confirmed by the statistical analyses. Paired t-tests comparing visual fixation time in the no music and music conditions show that music did not have an effect on engage-to-move ($t = 0.55, p > 0.05; N=24$) or grasp-to-disengage ($t = 0.71, p > 0.05; N=24$). Similarly, paired t-tests comparing reach duration time in the no music versus music conditions showed that music had no effect on time to complete the advance ($t = 0.83, p > 0.05; N =24$) or withdrawal ($t = 1.84, p > 0.05, N =24$) movements.

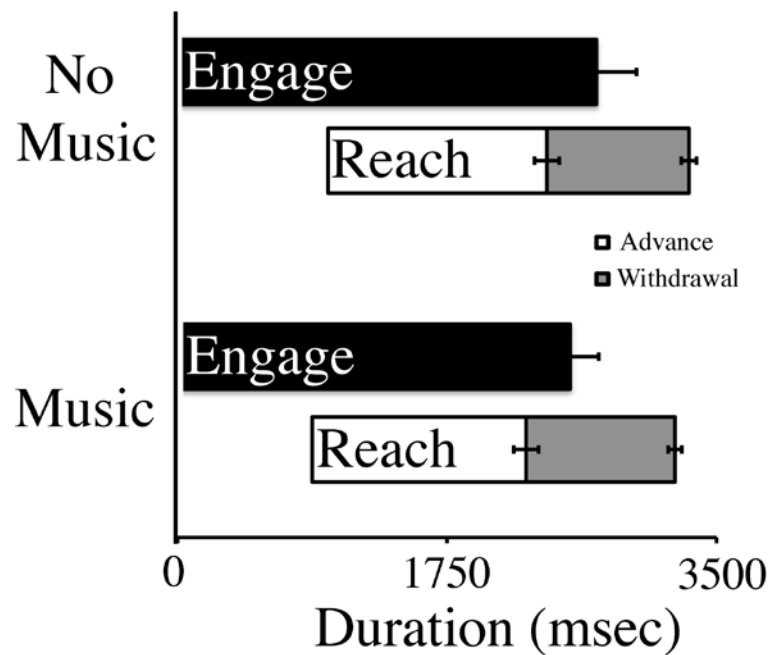


Figure 4. No music and music duration (mean and standard error in milliseconds) of visual fixation (engage) during the reach-to-eat (reach) movement for age-matched controls.

Movement scoring. A summary of the results of movement scoring of the age-matched control subjects in both the music and no music conditions are shown in Figure 5. There was no difference between the music and no music conditions for the

movement elements, with the exception of lift. The lift was likely impaired by hand tapping movements some subjects made to the music.

These main findings were confirmed by the statistical analyses. Paired t-tests comparing movement element scores in the no music and music conditions showed that music impaired lift compared to the no music condition ($t = 2.38$, $p < 0.05$, $N = 8$).

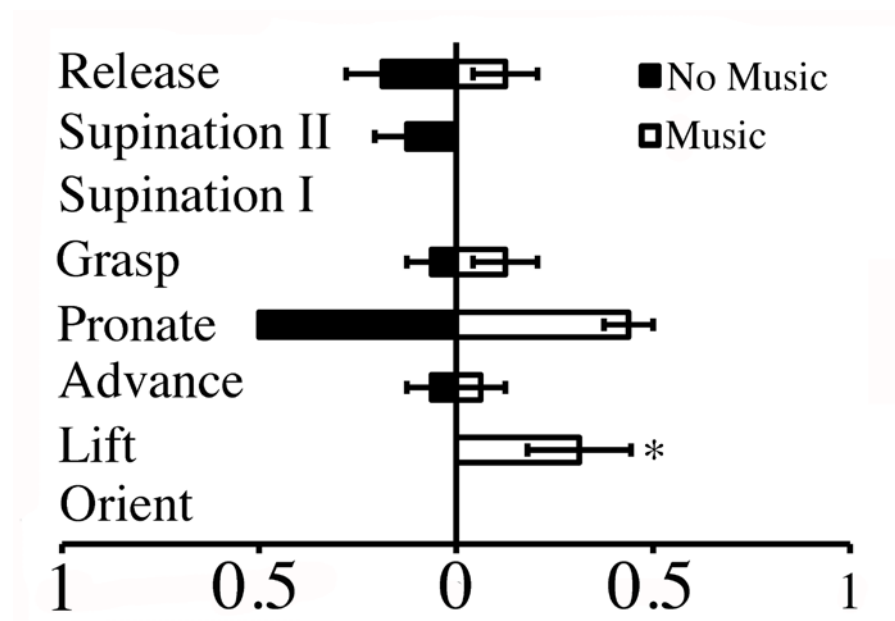


Figure 5. Movement component score (mean and standard error) for age-matched controls in the no music and music condition. * $p < 0.05$ Note. The impairment to lift in the music condition is a result of finger/hand tapping during the reaching trials.

Parkinson's Disease

Reach duration. A summary of the results of reach duration of the PD subjects in the no treatment, music only, drug only, and music and drug conditions is shown in Figure 6. There was no difference in the duration of the advance or the

withdrawal movements of the limb between any of the treatment conditions.

These main findings were confirmed by statistical analyses. A 2 x 4 ANOVA comparing movement time using arm (advance, withdrawal) and condition (no treatment, music only, drug only, music and drug) as within subject's measures resulted in a significant effect of arm ($F(1,23) = 83.30, p < 0.001$), but no condition ($F(3,69) = 0.34, p > 0.05$) or arm x condition ($F(3,69) = 2.00, p > 0.05$) effects.

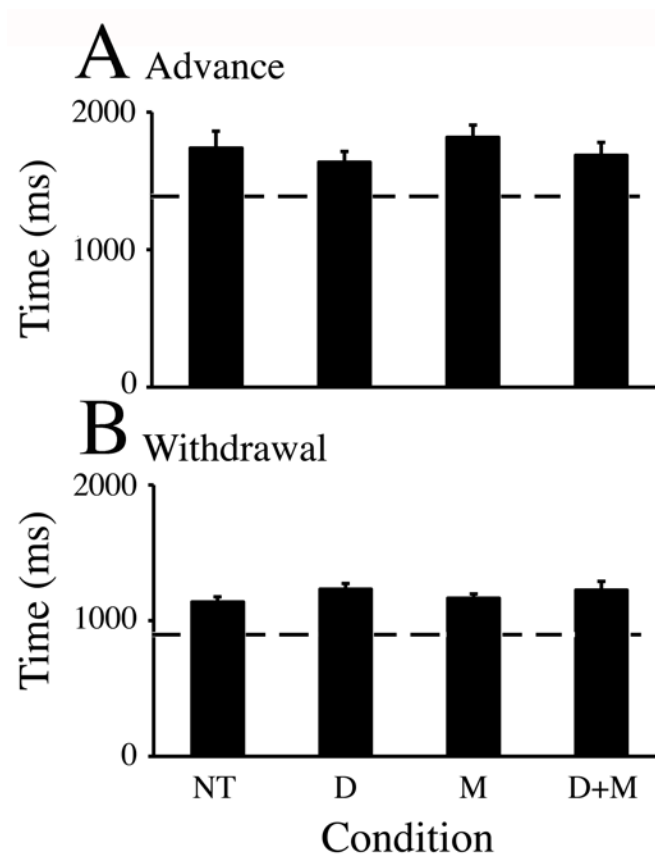


Figure 6. Duration (mean and standard error in milliseconds) of the (A) advance and (B) withdrawal movements for Parkinson's disease subjects in the four experimental conditions; NT = no treatment; D = drugs only; M = music only; D+M = drugs and music. The dashed line represents the mean of the age-matched controls. Note there are no significant differences between the four conditions.

Eye movement latency. A summary of the results of eye movement latency of the PD subjects in the no treatment, music only, drug only, and music and drug conditions is shown in Figure 7. Relative to the other testing conditions, the unmedicated PD continued to visually fixate the target for a prolonged duration as it was being withdrawn to the mouth for eating. That is, the PD subjects would look at the target as they grasped it and continue to look at their hand as they withdrew the food to the mouth. There was a difference between the no treatment and the treatment conditions in that music, drugs, and music and drugs decreased the duration of time for grasp-to-disengage. The decrease in latency was due to the fact that the eye disengaged from the target just as the fingers grasped it rather than to continue to watch the hand and target during the early part of the withdrawal movement.

These main findings were confirmed by statistical analyses. A 2 x 4 ANOVA on visual fixation time using eye (engage-to-move; grasp-to-disengage) and condition (no treatment, music only, drug only, music and drug) as the within subjects measures resulted in a significant effect of eye ($F(1,23) = 13.12, p < 0.001$), condition ($F(3,69) = 3.41, p < 0.05$), and eye x condition ($F(3,69) = 3.41, p < 0.05$). Post hoc showed that grasp-to-disengage decreased with music only ($p < 0.05, N = 24$), drugs only ($p < 0.01, N = 24$), and music and drugs ($p < 0.01, N = 24$) when compared to the no treatment condition.

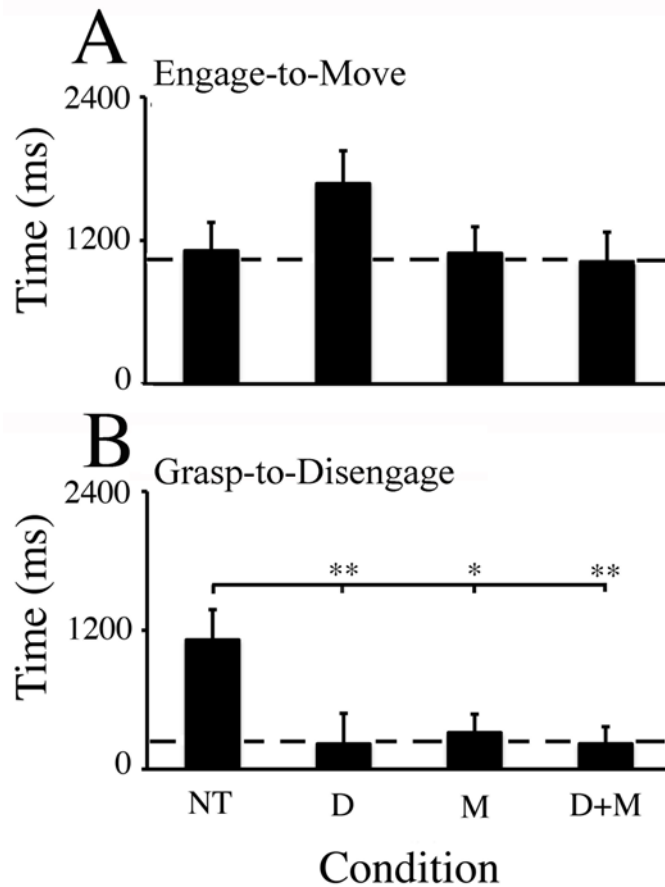


Figure 7. Duration (mean and standard error in milliseconds) of (A) engage-to-move and (B) grasp-to-disengage for Parkinson's disease subjects in the four experimental conditions; NT = no treatment; D = drugs only; M = music only; D+M = drugs and music. The dashed line represents the mean of the age-matched controls. Different from the no treatment condition at * $p < 0.05$; ** $p < 0.01$.

Movement scoring. A summary of the results of movement scoring of PD subjects in the no treatment, music only, drug only, and music and drug conditions is shown in Figure 8. There was no difference between the conditions for any of the movement components.

These main findings were confirmed by statistical analyses. An 8 x 4 ANOVA on movement score using element (orient, lift, advance, pronation, grasp, supination I, supination II, release) and condition (no treatment, music only, drug only, drug and

music) as the within subjects factors resulted in a significant effect of element ($F(4,49) = 7.21, p < 0.001$) and element x condition ($F(21,147) = 3.21, p < 0.001$), but no condition ($F(3,21) = 1.00, p > 0.05$) effect. Bonferroni corrections on post hoc analyses of the interaction were not significant.

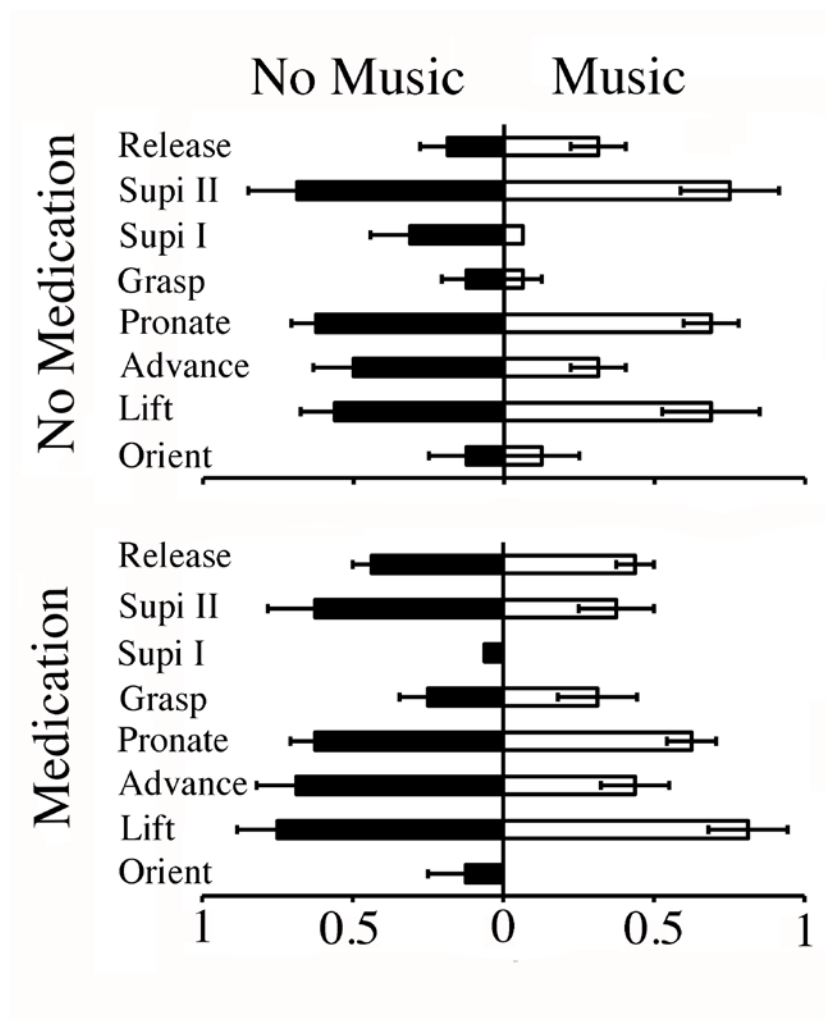


Figure 8. Movement component score (mean and standard error) for Parkinson's diseased subjects in the four experimental conditions. Note the absence of a treatment effect.

Age-Matched Controls vs. Parkinson's Disease

Reach duration. There was a difference in the duration of the advance and the withdrawal movement of the limb for the age-matched control subjects and PD subjects. The PD subjects took longer than age-matched controls to complete both the advance and withdrawal movements of the forelimb regardless of medication state, and medicated PD subjects did not differ from unmedicated PD subjects for duration of the reaching movement. Music did not affect the duration of the advance or withdrawal movements of the forelimb for age-matched controls or PD subjects regardless of medication state.

These main findings were confirmed by statistical analyses. A $3 \times 2 \times 2$ ANOVA on movement time using group (OAC, PD off, PD on) as the between subjects measure and arm (advance, withdrawal) and condition (no music, music) as the within subjects measures resulted in a significant effect of group ($F(2,69) = 9.79$, $p < 0.001$) and arm ($F(1,69) = 136.27$ $p < 0.001$) but no condition ($F(1,69) = 0.38$ $p > 0.05$), group $\times$ arm ($F(2,69) = 0.15$ $p > 0.05$), group $\times$ condition ($F(2,69) = 0.20$ $p > 0.05$), or group $\times$ arm $\times$ condition ($F(2,69) = 0.70$ $p > 0.05$) effects. Post hoc showed that PD off medication and PD on medication took longer than OAC to complete the reaching movement without music ($ps < 0.001$) and with music ($ps < 0.001$).

Eye movement latency. There was a difference in eye movement latency between the age-matched control subjects and PD subjects. Unmedicated PD subjects took longer than age-matched controls and medicated PD subjects to disengage from the target following contact of the digits with the target item. Music did affect eye

movement latency, in that medicated and unmedicated PD subjects took longer than age-matched controls to initiate a reaching movement towards a target after visual fixation.

These main findings were confirmed by statistical analyses. A 3 x 2 x 2 ANOVA on visual fixation time using group (OAC, PD off, PD on) as the between subjects factor and eye (engage-to-move; grasp-to-disengage) and condition (no music, music) as the within subjects measures resulted in significant effect of group ($F(2,69) = 5.38, p < 0.01$), eye ($F(1,69) = 20.89, p < 0.001$), condition ($F(1,69) = 4.39, p < 0.05$), and group x eye x condition ($F(2,69) = 5.63, p < 0.01$) but no group x eye ($F(2,69) = 1.29, p > 0.05$), eye x condition ($F(1,69) = 1.25, p > 0.05$), or group x condition ($F(2,69) = 0.95, p > 0.05$) interactions. Post hoc show that, without music, PD off medication took longer than OAC and PD on medication for grasp-to-disengage ($ps < 0.01$), and with music, PD off medication took longer than OAC and PD on medication for engage-to-move ($p < 0.001, p < 0.05$, respectively), PD on medication took longer than OAC for engage-to-move ($p < 0.05$).

Movement scoring. There was a difference in movement scoring for the age-matched control subjects and PD subjects. PD subjects were impaired in their reaching movements, especially in rotation of the wrist and grasping, regardless of medication state.

These main findings were confirmed by statistical analyses. A 3 x 8 x 2 ANOVA on movement score using group (OAC, PD off, PD on) as the between subjects factor and element (orient, lift, advance, pronation, grasp, supination I,

supination II, release) and condition (no music, music) as the within subjects factors resulted in a significant effect of group ($F(2,21) = 40.48, p < 0.001$), element ($F(7,147) = 15.85, p < 0.001$), group x element ($F(14,147) = 2.75, p < 0.001$), element x condition ($F(7,147) = 3.71, p < 0.001$) but no condition ($F(1,21) = 1.02, p > 0.05$), group x condition ($F(2,21) = 1.21, p > 0.05$), or group x element x condition ($F(14,147) = 1.70, p > 0.05$) effects. Post hoc showed that both PD off medication and PD on medication were impaired on the movement component rating scale compared to OAC ($ps < 0.001$).

Correlation between grasp-to-disengage and HY scores. A correlation between grasp-to-disengage of PD subjects off medication and their reaching scores was not significant. This was likely due to the relatively similar scores of the subjects, the small sample size, and the well-know lack of predictability between UPDRS scores and disease symptoms (Schallert, De Ryck, Whishaw, Ramirez, & Teitelbaum, 1979).

Discussion

This study provides the first comparison of the effects of medication and music on sensory attention shifting in skilled reaching by PD subjects. Age-matched control and PD subjects performed a seated reach-to-eat task, in which they reached for a piece of food and placed it in their mouth for eating, while biometric measures of eye movement and hand movement were collected. The PD group displayed enhanced visual attention of the reaching movement in that they visually fixated on the target for an increased duration following digit contact. The latency to visually

disengage the target decreased for PD subjects when tested with music, on drug therapy, and with a combination of both music and drug therapy. Impairments in reaching movements and slowed movement time in PD subjects were not improved by drug therapy and/or music. That music was as effective as drug treatment in normalizing the shift from visual attention to somatosensory attention may explain some of the ameliorative effects of music on movement in PD.

The objective of the present study was to make a systematic examination of the effects of music on sensory attention shifting by PD subjects on the reach-to-eat task. Both aged-matched control subjects and the PD subject's were tested in a home setting and selected two pieces of music by a favorite artist and these, played through an iPod, served as the music treatment. There have been previous reports of impaired sensory attention shifting in skilled reaching and its improvement with music, but in a number of respects these previous studies were incomplete. An examination of first admission unmedicated PD subjects (i.e. assessed following diagnosis with PD and prior to drug treatment) reported that the PD subjects displayed prolonged visual attention on the food target after it was contacted with the digits, but this was inferred from the video record as the study did not use biometric measures to track eye or hand movements (Doan et al., 2008; Melvin, 2005). In a study using eye tracking and biometric markers, more severely impaired PD subjects on medication were found to display prolonged visual attention both before and after the reach and visual attention was normalized by music (Sacrey et al., 2009). The latter study did not examine unmedicated PD subjects. The present study was designed to remedy the deficiencies in the experimental design of these previous studies. Thus, eye and hand movements were monitored with biometric measures and the PD subjects were tested in four

conditions: off medication, on medication, off medication with music, and on medication with music, and they were compared to OAC who were tested with and without familiar music.

Although the treatment conditions were administered in a systematic design, a number of *caveats* must be made with respect to the design of the study. Of necessity, the PD subjects were first tested in the unmedicated condition in the morning and then tested in the medicated condition in the afternoon. Future work might consider a balanced design in which groups of PD subjects were tested on medication first and when unmedicated second. Additionally, the music condition was presented after the non-music condition and it would be instructive to have PD groups that received the music condition first. Finally, the number of PD subjects was relatively small and future work could extend the analysis to a larger PD population. These weaknesses in the present study were related to patient convenience, the home testing methodology, and the availability of subjects who were not familiar and had not been exposed to music therapy. Nevertheless, given that the reach-to-eat movement is relatively unaffected by medication and other treatments in animal models of PD and in human PD subjects (see above), the present design was sufficiently robust to statistically demonstrate that sensory attention of the reach-to-eat movement is sensitive to treatment.

There was an impairment in visual attention in the reach-to-eat task for the unmedicated PD subjects. Other work has noted the importance of visual attention to appropriate grasping in PD subjects (Schettino et al., 2006). The present study shows that PD subjects also continued to visually attend the target after the food was

contacted, while the food was grasped, and as the hand carried the food item toward the mouth. By contrast, the control subjects visually fixated the target just before they initiated the reaching movement and then disengaged the target and looked away just as the food was contacted. For the control subjects, visual disengagement was usually associated with eye movements directed to some other part of the room, blinking, and a head movement that accompanied the altered gaze (de Bruin et al., 2008). For convenience, the period during which subjects visually fixated the target is referred to as the period of visual attention; the shift away of vision is referred to as visual disengagement, while the remainder of the movement is assumed to be guided by somatosensory attention. Thus, the impairment noted in the PD subjects was in shifting sensory attention from vision to somatosensation, presumably haptic attention of the digits in grasping and proprioceptive attention in bringing the hand to the mouth to release the food.

The impairment in sensory attention shifting from vision to somatosensation in the unmedicated PD subjects was reduced when the subjects were listening to familiar musical pieces. The sensory attention shifting impairment was also reduced in the medicated condition, and in the combined music and medicated condition. In all treatment (drugs, music, drugs and music) conditions, the PD subjects became similar to age-matched control subjects in that they visually fixated the target only during the advance movement. Thus, the results not only confirm that unmedicated PD subjects have an excessive reliance on visual attention, they also indicate that the shift from visual to somatosensory attention is improved by both music and drug treatment.

The excessive reliance on visual attention observed in the unmedicated PD subjects in the present study appears mild relative to the impairment reported for advanced PD subjects in previous work. Sacrey et al. (2008) report that medicated advanced PD subjects display exaggerated visual attention on the food target both before the initiation of the hand movement to reach as well as after the food target is contacted. Indeed, when scoring 'orienting to a target', one of the rating items on the reach movement component reaching scale, it is reported that providing a score for advanced PD subjects is difficult because the subjects stare at the location in which the food is to be placed both before the food is placed there and after the food has been placed there (Whishaw et al., 2002). It is possible that this visual fixation on a target is also symptomatic of the bradykinesia of PD. Nevertheless, other work (Sacrey et al., 2009; Whishaw et al., 2002) suggests that the enhanced visual attention to the target and hand during grasping and during withdrawal may serve a compensatory function to supplant impaired somatosensory attention of the hand.

Despite the improvement in visual attention resulting from music and/or drug treatment in the PD subjects, other impairments in the reaching movement were not improved. PD subjects were impaired in forelimb use, as assessed by the movement component rating scale, in that limb advance and withdrawal were abnormal and they used less rotation of the wrist and did not shape their digits appropriately to grasp the food. Parkinsonian subjects also display bradykinesia characterized by an increase in time to complete the reach-to-eat movement (Berardelli, Rothwell, Thompson, & Hallett, 2001; Sacrey et al., 2009). Treatment did not improve time to complete the movement or improve scores on the movement component rating scale for the PD subjects. These findings are consistent with previous work showing that motoric

impairments in skilled reaching are not improved by medication or music (Blin, Ferrandez, Pailhous, & Serratrice, 1991; Doan et al., 2006; Howe, 2003; Ma, Trombly, Tickle-Degnen, & Wagenaar, 2004; Melvin et al., 2005; Sacrey et al., 2009; Thaut et al., 1996; Whishaw et al., 2002).

It is unclear how familiar music acts to improve sensory attention shifting during reaching, but there are a number of possible explanations. First, there is evidence that music improves dopaminergic transmission (Blood & Zattore, 2001; Menon & Levitin, 2005; Panksepp & Bernatzky, 2002; Sutoo & Aklyama, 2004). According to this explanation, music and medication have similar positive effects through a direct effect on dopaminergic mechanisms associated with dopamine release in widespread regions of the brain including the frontal cortex. Second, music has been found to elicit increases in cerebral blood flow to the ventral striatum, amongst other brain structures (Blood et al., 2001). Through this action, music may have a general arousing effect. Third, it has been proposed that music may activate a nonspecific auditory arousal system, which in turn facilitates motor performance (Chomiak, Peters, & Hu, 2008; Hu, 2003). According to this explanation, the effects of music and dopamine medication may exert beneficial effects through different mechanisms and thus may be additive. This notion would be consistent with the finding of Sacrey et al (2009) that in advanced medicated PD subjects, music could still exert a beneficial effect on sensory attention of reaching.

The finding that music can normalize sensory attention shifting during reaching in PD subjects raises the interesting question of whether musical enhancement of sensory attention and sensory attention shifts may contribute to the

improvements in movement reported in other situations such as postural shifts, walking, dancing, or handling kitchen utensils (Schallert et al., 1979; Schallert & Hall, 1988; Woodlee, Kane, Chang, Cormack, & Schallert, 2008). For example, in normal walking, visual attention is directed to the terrain a few steps in advance of a present position, and stepping is accurate even though the immediate target of a step is not in view (Mohagheghi, Moraes, & Patla, 2004; Patla & Vickers, 1997; Patla & Vickers, 2003). A tendency to prolong visual attention on a visual feature during walking would likely impair the smooth flow of walking. It is possible that the freezing displayed by PD subjects, which frequently impedes walking, may be related to an impairment in visual disengagement. Music may have a beneficial effect on eye movements, and thus could contribute to improved walking. By facilitating visual disengagement, music may similarly improve performance in other tasks that demand frequent shifts in sensory attention (Posner & Raichle, 1994; Slavutsakaya & Shulgoyskii, 2007) including tasks that involve the manipulation of objects (Pacchetti et al., 2000). These ideas suggest that it would be interesting to monitor the eye movements in PD subjects engaged in other tasks and in subjects prone to freezing while walking.

In conclusion, the results of the present study show that unmedicated PD subjects have an impairment in sensory attention, in that they visually attend a food target for which they are reaching for a longer time after they have contacted and grasped it than do age-matched control subjects. Thus, they appear impaired in shifting attention from vision to somatosensory attention for food grasping and withdrawal of the food to the mouth. Sensory attention shifting is normalized both when PD subjects are listening to a favorite piece of music and have received

pharmacological medication. Other impairments of the reach-to-eat movement were unaffected by drugs or music. The main finding in the present study is thus generally consistent with studies suggesting that music can act to improve the performance of PD subjects. The present results, if generalizable to other tasks in which shifts in sensory attention are required, may provide one explanation for the beneficial effects of music on movement.

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Chapter 5:

**Proximal Movements Compensate for Distal Movement Impairments in a
Reach-To-Eat Task in Huntington's Disease: New Insights into Motor
Impairments in a Real-World Skill**

Abstract

Huntington's disease (HD) causes severe motor impairments that are characterized by chorea, dystonia, and impaired fine motor control. As yet, there has been no comprehensive assessment of the impairments in skilled arm, hand and digit movements as they are used in every day tasks. The present study investigated the reaching of twelve HD subjects and twelve age-matched controls on a reach-to-eat task in which all subjects reached for a small food item and then brought it to the mouth for eating. The task assesses the major features of skilled forelimb use, including orienting to a target, advance of the hand to a target, use of a precision grasp of the target, limb withdrawal to the mouth, and release of the food item into the mouth. The movements were analyzed frame-by-frame by scoring the video record using an established movement element rating scale and by kinematic analysis to describe limb trajectory. HD subjects displayed many impairments in all components of reaching and displayed extremely variable performance between subjects. All HD subjects displayed greater reliance on more proximal movements in reaching. They also displayed overall jerkiness, a significant impairment in end point error correction, deficits in timing and terminating motion (overshooting the target), impairments in rotation of the hand, abnormalities in grasping, and impairments in releasing the food item to the mouth. The quantification provided by this analysis provides new insights into the impairments of HD subjects, provides an easily administered and inexpensive way to document the many skilled limb movement impairments, and relates the impairments to a real-world context. The protocol can serve as a useful clinical tool to evaluate innovative therapeutic interventions in HD such as physiotherapy, drug therapy, or functional neurosurgical procedures

Huntington's disease (HD) is a neurodegenerative, genetic disorder resulting in cognitive and psychiatric deficits, as well as abnormal movements (Myrianthopoulos, 1966; Pearson & Petersen, 1954). The impairments in movement are characterized by chorea, dystonia, and impaired fine motor control. The pathology typically starts in the caudate and putamen (striatum), selectively affecting the enkephalin-containing GABAergic medium spiny neurons (Albin Reiner, Anderson, Penney, & Young, 1990; Albin, Qin, Young, Penney, & Chesselet, 1991). These neurons are part of the basal ganglia's indirect pathway and this cell loss (i.e. loss of GABA) results in disinhibition of the thalamus. In turn, disinhibition is thought to contribute to choreatic symptoms (Penney Jr. & Young, 1983). In its later stages, the disease spreads to other parts of the brain, including the direct pathway of the basal ganglia and cortical areas that are part of the cortico-striatal circuits involved in the planning and execution of voluntary and goal-directed movement. Although there have been significant advances in diagnosing HD (e.g. genetic testing), there is still a need for standardized tests that can be used in both the clinic and laboratory to document the motor impairments caused by the disease and treatment of the impairments.

Motor impairments of HD have been studied in laboratory-based tasks, and include deficits in the control of the arm and hand. There are a number of alterations to arm movement including temporal features (i.e. time-to-peak acceleration, velocity, and de-acceleration), movement termination, and accuracy in grasping a target (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992; Bonfiglioli, De Berti, Nichelli, Nicoletti, & Castiello, 1998; Fellows, Schwartz, Domeges, & Noth, 1997; Smith, Brandt, & Shadmehr, 2000). Movement initiation and early grasp formation are reported as less affected. Generalizing from this work, it would be expected that

impairments in the control of the arm would contribute to the difficulty in carrying out real world-tasks but yet no such assessment has been made. One such real-world forelimb task is using the hands to pick up food items for eating, and this movement can be modeled by a reach-to-eat task (skilled reaching task). For the task, a subject lifts the hand from the lap, reaches for a small food item located on a pedestal, places the food in the mouth for eating, and then replaces the hand on the lap. The task captures the major forelimb movements of limb advance, grasping, and withdrawal as they have been defined by functional analysis of motor cortex (Meier, Aflalo, Kastner, & Graziano, 2008). A rating scale and biomechanical analysis obtained frame-by-frame from video recordings are used to evaluate visual attention to the target, limb advance and hand shaping for grasping, limb withdrawal and hand shaping to release the food into the mouth, and the return of the hand to its starting location. This task is an inexpensive, simple, and naturalistic method for investigating fine motor control, has been validated in both human and non-human subjects, and has been used for assessing treatments for animal models of HD (Dobrossy & Dunnett, 2006; Whishaw, Zeeb, Erickson, & McDonald, 2007). The utility of the task is that it can be given in a clinical setting along with other standard assessment procedures. A single reach can provide objective results, the test is not physically demanding for the patient, and performance can be quickly and objectively scored. Therefore the task is potentially useful for evaluating upper extremity use in performing skilled acts as a function of disease status and treatment (Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Metz & Whishaw 2000; Sacrey, Clark, & Whishaw, 2009; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002).

The purpose of the present chapter was to document the reaching movements of HD subjects in a real-world, functional, and goal-directed setting. Twelve HD subjects and twelve age-matched controls were tested with video recording during regular attendance at a movement disorders clinic. All subjects performed the reaching-for-food task with the left and the right hand, and their performance was scored by frame-by-frame analysis of the video record using a movement element rating scale. The video record was also used to construct a kinematic description of motor deficits using Peak Motus technology to reconstruct hand and elbow movements. The present study presents new insights into the everyday functional deficits in HD patients and also provides an easy, sensitive, and inexpensive protocol to analyze motor behavior in patients suffering from HD.

Material and Methods

Subjects

Huntington's disease subjects were recruited from the University of Freiburg (5 males and 7 females; ages 44.0 ± 7.6 years; UHDRS 34.8 ± 10.5). For HD subject characteristics, see Table 1. During regular visits, a trained neurologist assessed the disease severity using the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996). The motor task examined in this study was part of a larger examination of both motor and cognitive impairment. Age-matched middle-aged adult control subjects were recruited from the cities of Lethbridge, Alberta, Canada and Cardiff, Wales, United Kingdom (6 males and 6 females; ages 43.7 ± 5.7 years). There was no significant age difference between the two groups ($p = 0.90$). All control subjects were self-reported to be of good health with no history of

neurological disorder, and all subjects had normal or corrected to normal (contact lens) vision. The University of Lethbridge Human Subject Research Committee and the local ethical board of the University of Freiburg jointly approved the study. Informed consent was obtained from subjects prior to initiation of the testing session. The study was conducted in accordance with the Declaration of Helsinki.

Table 1. Huntington's disease subjects characteristics

ID	Age	Sex	Duration	UHDRS
1	36	M	2	25
2	50	M	7	37
3	40	F	10	30
4	38	F	3	49
5	49	F	UN	43
6	54	M	3	19
7	31	M	4	44
8	54	F	15	32
9	48	F	5	20
10	39	F	UN	38
11	40	M	5	30
12	49	F	5	50
Mean	44 ± 7.6	5 Males	5.9 ± 3.9	34.8 ± 10.5
	years	7 Females	years	

Reaching Task

Subjects performed a seated reach-to-eat task as shown in Figure 1, in which they reached toward a pedestal for a small food item that they grasped and advanced to the mouth for eating (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008; Melvin et al. 2005; Whishaw et al. 2002). Subjects were seated in a comfortable upright position, with their feet flat on the floor. A self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized

to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° extension) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion).

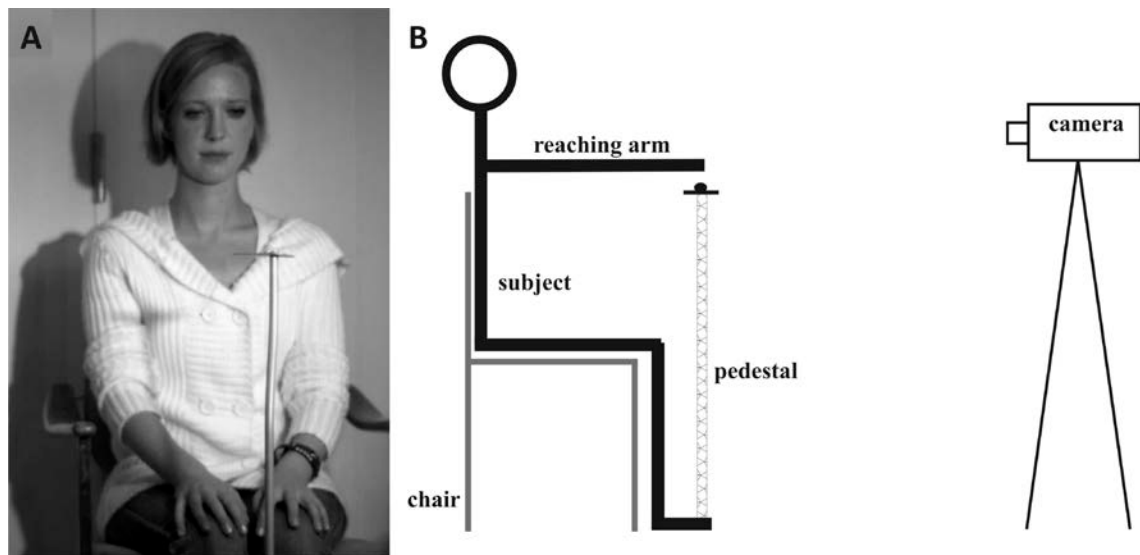


Figure 1. Experimental set-up. (A) Food is placed on the pedestal and the subject begins a reach with hand open on the lap. (B) Schematic view of the reaching task. Subjects are asked to sit comfortably. The pedestal was positioned an arm length away with the elbow fully stretched to 180 degrees. The height of the pedestal was adjusted to each subject's trunk height. The reaching movement was filmed from a frontal view.

Video-recording and Playback

Subjects were filmed from a frontal perspective to score the movement element components (see below) and from a lateral perspective to score movement trajectories (see below). All images were captured with a conventional video camera (Canon ZR 850 NTSC; www.canon.ca), which captures images at 30 frames per second and with a shutter speed of 500 frames per second. The video-records were

analyzed by frame-by-frame playback using a Sony Mini DV digital video cassette recorder (Model number GV-D1000 NTSC, www.sony.ca).

Reaching Instructions

Once subjects were seated, they were asked to place their hands palm down on their thighs. The experimenter stood to the left of the subject (i.e. in peripheral visual space) and placed a food item (Cheerio™ or Haribo Gummy Bear™) on the pedestal for each trial. The subjects were instructed to perform reaches with both their hands, first the right hand and then the left hand. Each testing trial was initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure. Each trial concluded following successful placement of the food item in the mouth and return of the reaching hand to the lap. Because control subjects always replace the hand at the starting position on the lap, appropriate placement of the hand was a dependent variable. The experimenter maintained a casual relationship with the subjects, e.g. engaging in conversation between reaches, in order to maintain a quasi-natural testing condition. Each subject completed three reaching trials with their right hand and three reaching trials with their left hand.

Movement Element Measurement

The reach-to-eat movement was measured using a modified version of the movement element rating scale (Melvin et al, 2005; Whishaw et al., 2002). The scale is based on analysis of each limb segment’s movement in relation to its more proximal segment. The score of a limb segment’s movements can identify both changes in a segment’s movement and the compensatory movements of adjacent limb

segments. As is illustrated in Table 2, the following measures were assessed from frame-by-frame replay of the video record: (1) Orient – head and eyes orient to the target prior to arm and hand movement; (2) Lift – supination of the hand following lift from the lap; (3) Advance – the forelimb moves towards the target; (4) Pronation - pronation of the hand over the food item; (5) Grasp – arm remains still as digits close around the food item; (6) Supination I – hand rotates immediately following grasp; (7) Supination II – hand rotates as hand/food nears the mouth; (8) Release – food is placed in the mouth and the hand is lowered for the next trial. A score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent. For the present study, reaches were scored independently by two investigators (LS and AK) but because the results were highly correlated, the scores present in the results were those from one rater (AK).

Table 2. Movement Element Rating Scale

Component	Element	Sub-Element	Description
Orient	Orient	A	Head is moving freely then fixes on target at beginning of trial
		B	Eyes locate target prior to movement of hand/reach
Transport	Lift	A	Initial hand lift due to flexion of the elbow
		B	Digits semi-flex
		C	Hand supinated approximately 30 degrees
		D	Tips of digits are brought towards the midline of the body
	Advance	A	Hand takes shortest path to target
		B	Hand stops directly above the target
		C	Trunk leans to the side opposite reach
	Pronation	A	Digits open and extend over the food target
		B	Knuckle on reaching hand forms horizontal line
		C	Elbow opens to full arm length as subject reaches
Grasp	Grasp	A	Thumb and index finger grasp food item
		B	Digits 3-5 remain still as grasp is executed
		C	Wrist extends to lift food item from platform
Withdrawal	Supination	A	Reaching hand supinates 45 degrees immediately after verticle lift
		B	Hand supinates another 45 degrees when in close proximity to the mouth
Release	Release	A	Head turns to meet food
		B	Finger tips contact lips for placement of food item in mouth
		C	Digits open to release food item into mouth
		D	Hand takes shortest path back to lap
		E	Hand is placed on lap with fingers extended and palm down
		F	Trunk leans back towards midline

Kinematic Analysis

A representative reach from the subjects were captured with Final Cut Express HD (V.3.5; <http://www.apple.com>) and analyzed by the frame-by-frame motion measurement software ‘Peak Motus’ v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) with an output of 30 Hz. The data were acquired via a manual mode, digitizing the moving points by cursor. Representative limb trajectories were reconstructed on a Cartesian diagram. In addition, the degree of hand rotation and elbow angle were analyzed during the advance (reach-to-grasp) phase from the start position on the lap until the digits contacted the food item. A virtual horizontal line served as the baseline to which hand

rotation was measured (virtual line through the first and second knuckle). Elbow angle was measured using the angle between (a) the shoulder and the elbow and (b) the hand and the elbow. Time for the control subjects was normalized to the speed of the (slower) HD subjects.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v 17) repeated measures ANOVA to compare age-matched controls to HD subjects. Bonferroni corrections were done on post hoc analyses. A *p* value of 0.05 was used to determine statistical significance.

Results

Movement element analysis of the reach-to-eat movement and kinematic analysis indicated that the HD group was impaired on the reach-to-eat movement compared to age-matched controls. The results are described fully below for the component description, the movement element analysis, and the kinematic analysis of the movements.

Component Description

The HD subjects were always able to successfully use either their left or their right limb to advance their hand to the food item, to grasp it using a pincer grasp, to withdraw their limb and release the food into the mouth, and to replace the limb on the lap without instruction. Nevertheless, the reaching movement featured

abnormalities relative to the movements made by the age-matched control subjects. Table 3 provides a summary of behaviors in which the movements were abnormal, e.g., exaggerated, absent, or located at an inappropriate time in the reach, or were altered by choreatic movements intruding into the reaching movement. Table 3 indicates that the subjects were very variable in the alterations in reaching movements that they displayed. Nevertheless, there were some deficits that were featured in the majority of the subjects. The HD subjects tended to use more proximal body and limb segments than do control subjects at each movement phase. For example, they used the trunk and head to compensate for impairments in directing the hand to the target and mouth and they relied more on upper arm movements in lifting and directing the hand. The HD subjects were also impaired in ending each movement element of the reach and so the reach had the character of exaggerating each movement element. For example, when advancing the limb to the food, they might fully extend the limb, when shaping the digits they might extend or flex the digits in an exaggerated way, and when flexing the limb that movement might also be exaggerated. The HD subjects also displayed a strategy using tactile information to assist in completing the movement. For example, when grasping the food they might support their hand with one or more digits on the pedestal, rather than simply releasing the food into the lips, they inserted their fingers with the food into the mouth, and when replacing their hand on the lap they might first contact the lap with the digits and from there reposition the hand. Finally, the more severe HD subjects made many choreatic movements of the body which complicated making a smooth reaching movement as the arm and hand attempted to compensate for the displacement of the body. These impairments are quite variable from subject to subject, likely because there were subject differences in the disease severity. These features of the reaches of HD subjects compared to their

age-matched controls are described in relation to the component movements of the reach:

Table 3. Behaviors that are abnormal in HD subjects

Behavior	1	2	3	4	5	6	7	8	9	10	11	12
Orient to target	x	x	x		x		x	x		x		x
Disengage from target	x		x	x		x	x				x	x
Support trunk	x			x								
Shaping (early/late)			x		x	x		x				x
Support grasp		x			x		x	x				x
Head posture	x		x	x	x	x	x	x			x	x
Digit in mouth	x	x	x	x	x	x		x			x	x
Lap adjustment	x	x		x	x	x			x		x	x
Hand on lap	x				x	x		x	x	x		x
Choreatic		x	x	x	x		x	x			x	

x: behavior is exaggerated, absent, or located at an inappropriate time during the reach

Orient. Control subjects do not orient their head and eyes to the target until just before they initiate the reach. They then visually attend the target throughout the period of limb advance to the target and disengage the target by blinking and looking away just as they grasp the target. The performance of the HD subjects was more variable in that four of them oriented like controls and eight HD subjects displayed exaggerated visual attention on the food item prior to initiating the reach, and seven of them continued to look at the target as they withdrew the target to the mouth. Three of the subjects also disengaged and then reengaged the target as they advanced the hand to it. The impairments displayed by the HD subjects were not obviously related to their UHDRS score or the severity of their movement impairments.

A) Control



B) Huntington's Disease



Figure 2. Superimposed images of the left reaching hand of a control (left) and a mild HD (right) subject. Note the location of the elbow for the control and HD subject.

Advance. To move their hand to the target, control subjects initiate the reach at the hand and flex their lower arm and elbow to lift the hand from the lap. They then semi-flex the digits and supinate the hand as they lifted and raised the hand to an aiming position, following which they extend the elbow to bring the digits to the target. At the completion of the aiming movement and as the hand approaches the target, the digits are shaped for grasping. Lifting and advancing the limb is assisted by a shift of the trunk away from the reaching limb. Thus, as illustrated in Figure 2A, the elbow remains on the same mediolateral plane throughout the reach. The HD subjects passively lift their hand from their lap by flexing and abducting the elbow. Figure 2B

illustrates the outward location of the elbow. The HD subjects tended not to semi-flex the digits or rotate their hand during advance, but the hand was passively pronated with the lift. The HD subjects did shape the thumb and forefinger to grasp, but six subjects began shaping the hand well before aiming, as the hand was lifted, and two subjects only began shaping the digits when they reached the target. In addition, the non-grasping digits often were extended or flexed to an exaggerated extent. The HD subjects did assist limb lifting and advance by making a compensatory contraversive movement, but the movement tended to be exaggerated so that the reaching hand approached the target from a more lateral position that was observed in the control subjects. The exaggerated movement of the arm in the lateral and medial plane relative to control subjects can thus be observed in Figure 2.

Grasp. Control subjects grasp the food with the thumb and index finger and digits 3 through 5 flex and close as the object is grasped (Figure 3 A-C). The wrist extends to lift the target from the pedestal. HD subjects grasped the food with the thumb and index finger and close the other digits when grasping. Nevertheless, the digits displayed abnormal postures and digits 3 through 5 serve as leverage on the pedestal to assist with grasp for half of the HD subjects (Figure 3 D-F). The hand is lifted from the pedestal with the lower arm and abduction of the elbow.

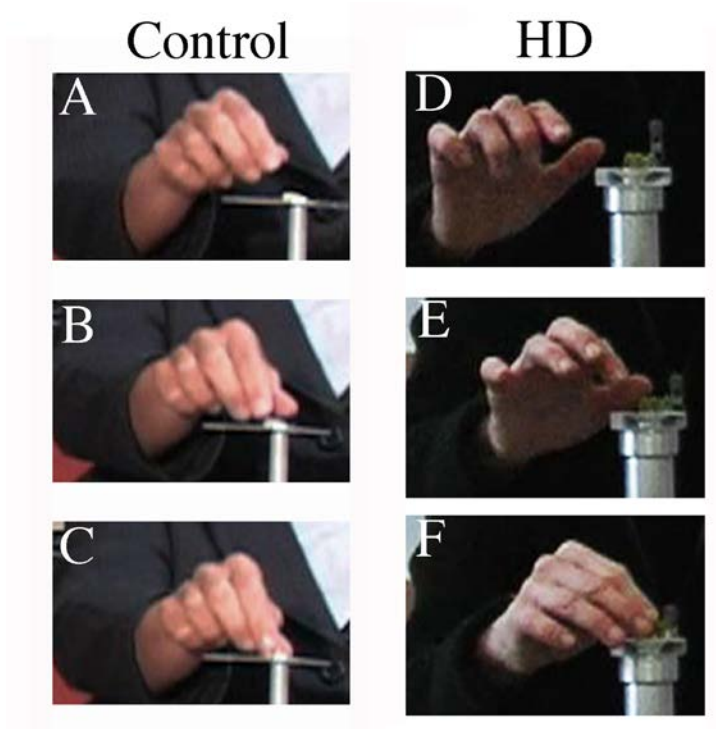


Figure 3. Representative photographs from a control (A-C) and HD (D-F) subject grasping a small food item. Note the early shaping of the digits and use of digits 3 and 4 to assist the grasp for the HD subject.

Withdrawal. Control subjects supinate the hand by about 45 degrees in supination I, as the hand is lifted with the food (Figure 4 A). As the hand approaches the mouth, it again supinates by about 45 degrees in supination II, to place the grasping digits in close proximity with the lips (Figure 4 B). As the hand approaches the lips, the trunk shifts to its starting upright position so that the head and lips meet the approaching hand. The HD subjects show little supination I when the hand is lifted (Figure 4 C) and little supination II as the hand approaches the mouth (Figure 4 D). Three of the more severe HD subjects displayed a break in their withdrawal movement between supination I and supination II, even to the point of lowering the hand to the lap. In addition, seven subjects displayed less synergistic movement between the hand and the mouth because the head did not meet the hand to prepare

for release but rather either chased the hand or withdrew from the hand. For three subjects the choreatic movements intruded on the smooth movement of the hand to the mouth.

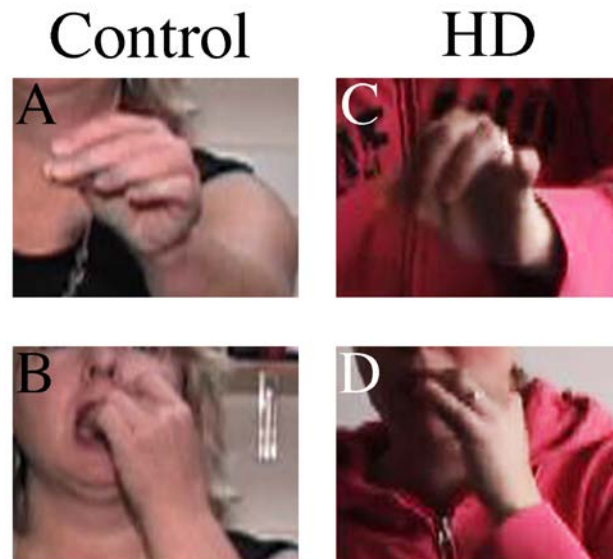


Figure 4. Representative photographs from a control (A-B) and HD (C-D) subject withdrawing the hand to the mouth. Note the location of the back of the hand for the control and HD subject for supination I (A and C) and supination II (B and D).

Release. Control subjects bring the food item to the lips and open the digits to release the food as the lips close to grasp the food item (Figure 5 A). Nine of the 12 HD subjects placed their digits in their mouth and closed their lips around their digits to release the food item into the mouth (Figure 5 C). After the food item is released, the control subjects lower the hand and place it on the starting position on the lap (Figure 5 B). Through the course of the movement, the hand moves from the supinated position with the digits closed and flexed to a pronated position with the digits extended and open. The HD subjects also lower their hand to the lap but the path the hand takes to the lap is quite variable. In addition, the digits might first contact the lap following which the posture and the hand is adjusted to take a start position (Figure 5 D). One of the HD subjects pushed the hands against the lap in an

apparent strategy to supporting the trunk upright while one HD subject wrapped the hands around the midsection and flexed the trunk forward before and after each reach.

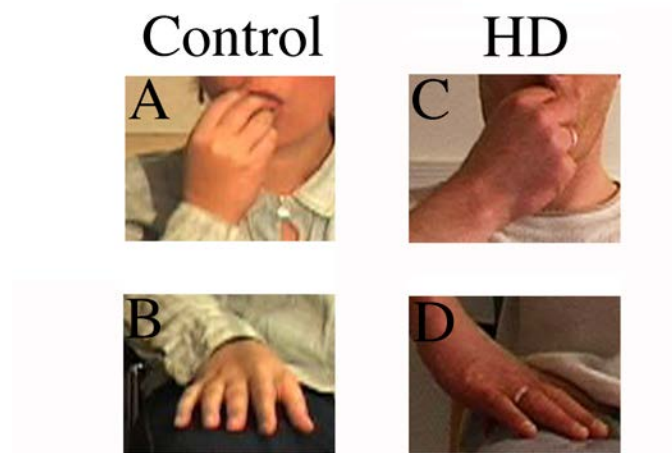


Figure 5. Representative photographs from a control (A-B) and HD (C-D) subject for release of the food item into the mouth and return of the hand to the lap. Note how the HD subject places the digits into the mouth and touches the lap with his fingertips prior to placement of the hand on the lap.

Movement Element Analysis

As displayed in Figure 6, HD subjects were more impaired than control subjects on the movement element rating scale. These findings are supported by a 2 X 2 X 7 ANOVA on movement score using group (controls, HD) as the between subjects factor and hand (left, right) and element (orient, lift, advance, pronation, grasp, supination, release) as the within subjects factors resulting in a significant effect of group ($F(1,22) = 272.73, p < 0.001$), hand ($F(1,22) = 5.02, p < 0.05$), element ($F(6,132) = 26.65, p < 0.001$), and Group x Element ($F(6,132) = 18.21, p < 0.001$), but no Group x Hand ($F(1,22) = 0.01, p > 0.05$), Hand x Element ($F(6,132) = 1.88, p > 0.05$), or Group x Hand x Element ($F(6,132) = 0.82, p > 0.05$) interactions. The HD group was more impaired than the control group for lift, advance, pronation, grasp, supination, and release (all $p < 0.001$).

Kinematic Analyses

Hand rotation and elbow flexion of control and HD subjects from start to grasp are shown in Figure 7. Control subjects supinate their hand following lift from the lap and pronate their hand over the target to assist grasp. Huntington disease subjects do not supinate their hand following lift from the lap or pronate their hand to assist grasp. Pronation of the hand over the food target is accomplished through rotation of the elbow. Control subjects flex their elbow at the start of the reaching movement and gradually open the elbow to full extension to assist with the grasp. Huntington disease subjects elbow is extended at the start of the reaching movement and remains extended to the grasp.

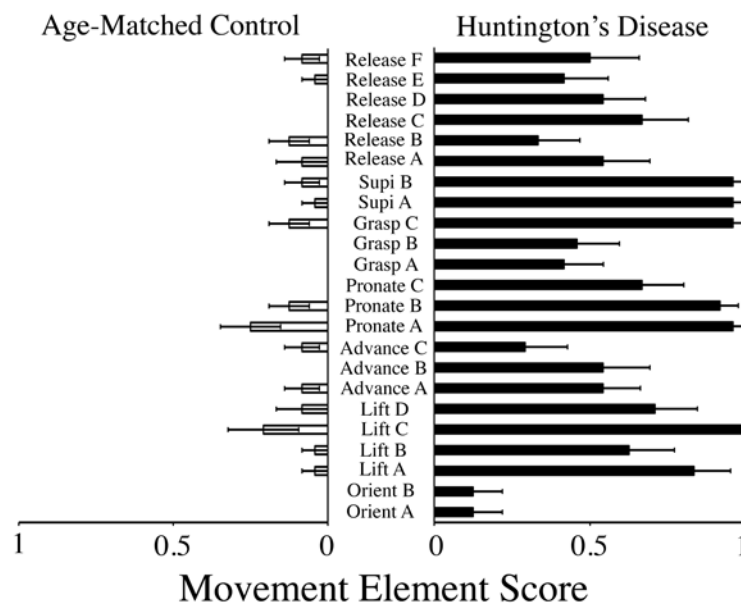


Figure 6. Movement element score results for control (left) and HD (right) subjects. A score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent. Both groups were significantly different ($p < 0.001$). All sub-scores of the elements Lift, Advance, Pronate, Grasp, Supination, and Release were significantly impaired for the HD subjects (all $p < 0.0001$).

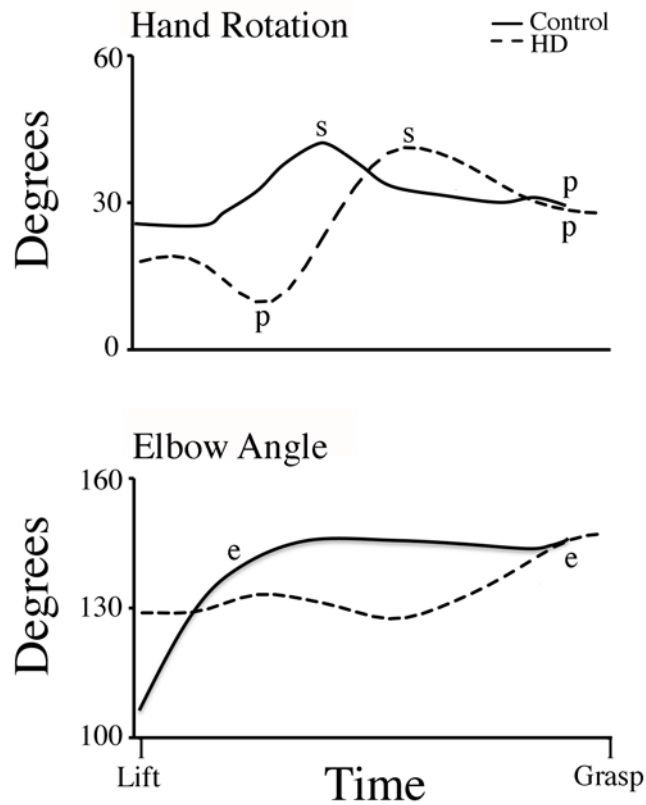


Figure 7. Kinematic analyses of Hand Rotation and Elbow Angle change during a reach-to-grasp movement. Time for the control subjects was normalized to the speed of the (slower) HD subjects (s = supination; p = pronation; e = extension).

A frame-by-frame trace of the trajectory of hand and elbow movements of a control, a mild HD subject and a severe HD subject are visualized in Figure 8. The control subject displays a smooth trajectory for both the hand and the elbow. Both trajectories have a mostly vertical orientation. The mild HD subject shows relatively mild impairments in hand movements, although the bell-shaped grasping pattern (indicating hand rotation; Figure 8 B, see at and before ‘G’) is almost absent. Interestingly, the elbow movements are severely impaired compared to the control subject. Motion direction is horizontally oriented; the elbow starts moving from a higher and more lateral starting position, and the trajectory is not smooth but the

elbow seems to make many adjusting or mildly choreic movements. The severe HD subject suffers from severe chorea in both the hand and the elbow. Although the subject reaches for the food item at first attempt, withdrawal and release need three attempts.

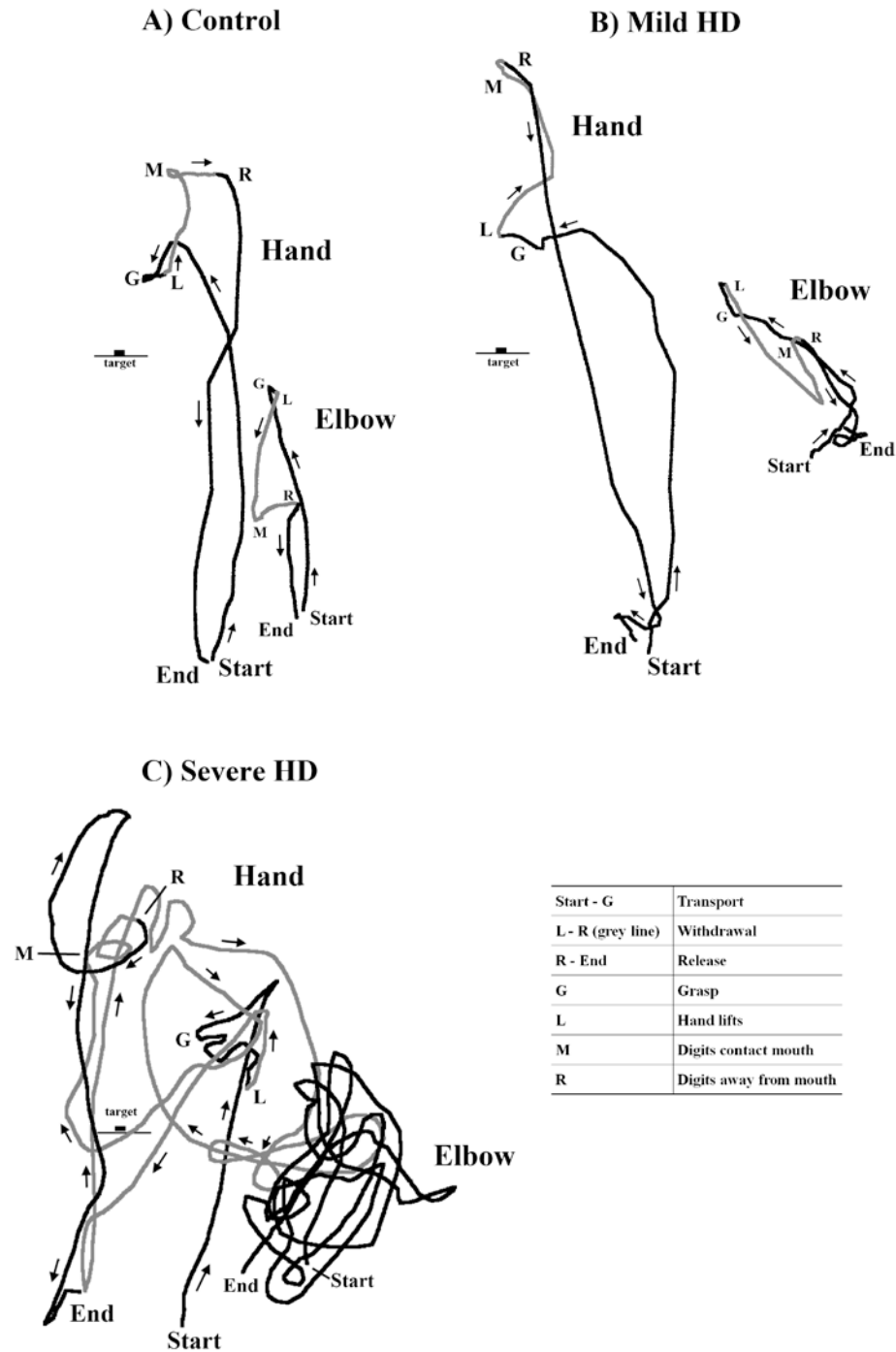


Figure 8. Hand trajectories of (A) a control, (B) a mild HD, and (C) a severe HD subject. Note the relatively normal hand trajectory in mild HD. Elbow movements, in contrast, are impaired and compensate for motor deficits in the hand.

Discussion

This study provides the first description of skilled movements of HD subjects in the reach-to-eat task. Twelve age-matched controls and twelve HD subjects were video-recorded while performing a seated reach-to-eat task in which a hand is advanced to a small food item that is grasped and brought to the mouth for eating. The effects of HD on motor performance were scored with a modified reaching scale based on a frame-by-frame analysis of a single reach (Melvin et al. 2005; Whishaw et al. 2002). The HD subjects were surprisingly variable in their performance and all displayed many abnormalities in each phase of the reach, including little rotation of the hand, digit shaping for grasping occurring at an incorrect time during the reach, and impaired temporal sequencing of movements and movement termination. Consistent impairments were that the subjects compensated by using more proximal body segments in performing the reach movements than did the control subjects, and they were also impaired in making transitions to the successive movement components of a reach. Choreatic movements also intruded on the smooth flow of the reach. The results demonstrate that the analysis of reach-to-eat movements in an analogue of a goal-directed real-world task provides an easily administered, inexpensive, and sensitive tool to examine impairments in motor pattern sequencing in HD.

The task used in the present study is very useful for a number of reasons. First, it assesses a wide range of upper limb functions as they are used in an every-day real world situation. The movement involves visual attention, limb advance, hand-shaping for precision grasping, limb withdrawal, and target release. Thus, the task assesses most of the movement primitives of the upper limb as they have been identified by

analysis of motor cortex function (Meier et al. 2008). Second the task is easy to administer, can be given in the clinic or the laboratory, and will not fatigue a subject who might be undergoing other clinical assessments. Thus, the task can be administered in repeated assessment and treatment situations. Third, the results can be subjected to comprehensive and detailed end point, movement element, and biometric analysis allowing robust inter and intra-subject contrasts. The analysis can consist of movement element scoring that can be derived by a few minutes of frame-by-frame analysis of the video record and/or more comprehensive biomechanical analysis of the video record. In addition, the video record can provide documentation of the course of the disease and the effects of treatment. It is not surprising that the test reveals a between subject heterogeneity that likely reflects the variable between subject anatomical abnormalities and course of the disease (Thu et al., 2010), as well as revealing some commonalities in the motor impairments. Finally, we propose that the reach-to-eat assessment will prove useful in monitoring treatment effects, as has been documented in preclinical studies (Dobrossy & Dunnett, 2008; Mazzocchi-Jones, Dobrossy, & Dunnett, 2009; Seo, Kim, & Isacson, 2008), especially because very similar testing and scoring of skilled reaching has been developed for preclinical research. The following sections discuss some of the impairments displayed by the HD subjects on the reach-to-eat task.

Reach initiation was impaired for HD subjects in a number of ways. Control subjects initiate a reaching movement through flexion of the wrist to lift the hand from the starting position on the lap. The HD subjects flex their elbow to initiate a reach and the hand is carried passively from the start position by movement of the upper arm. This is in contrast to earlier observations by Bonfiglioli et al. (1998) who reported that the beginning of a movement was normal in HD. This difference may be

related to the different procedures used in the experiments. Bonfiglioli et al. used a laboratory-based task that did not require the limb to be raised and advanced to an aiming position, as was required in the present study. Thus, a strength of the present task is that the movement is initiated from a resting position as is more typical of a real-world situation.

Distal movements of the hand and digits were also affected in a number of ways in HD. The HD subjects generally did not supinate their hand during lift, pronate the hand during advance, or supinate the hand after grasping the food. These rotational movements are typically achieved by rotation at the forearm. The absence of hand rotation was compensated by exaggerated shoulder and elbow movements, in which the elbow would over-extend or over-rotate to bring the hand to the correct spatial location. This compensatory strategy became more exaggerated in the severe HD subject's; in which chorea impairs the ability to make smooth voluntary movements because involuntary body movements contribute to the abnormal trajectory of the limb.

The HD subjects did shape their hand for grasping, but digit shaping occurred at an incorrect location during the reach relative to control subjects. Control subjects shaped their digits to grasp after the limb is lifted to an aiming position and as the limb is advanced to the target, and digit shaping is completed as the hand is pronated before reaching the target. In HD subjects, shaping of the pincer grasp, using the thumb and forefinger was present; however, the majority of HD subjects shaped their digits for grasp too early or too late, either during advance of the limb to the target or just prior to tactile contact with the target. That shaping of the digits to make the pincer grasp is present is interesting. It is proposed that the parietal cortex is involved

in digit shaping and that vision is importantly involved in ‘on-line’ shaping (Culham et al., 2003; Goodale, Westwood, & Milner, 2004). Thus, there may be less basal ganglia involvement in this aspect of the reach (Rizzolatti, Luppino, & Matelli, 1998). During premanifest and early HD, striatal atrophy is thought to be one of the first changes that occur (Paulsen et al., 2006). Recent imaging studies, however, observed sub-cortical and cortical atrophy in early HD subjects including the parietal cortex (Hobbs et al., 2010; Rosas et al., 2006). Hobbs and colleagues postulate that this more widespread degeneration leads to a loss of structural connectivity, which then contributes to (motor) symptoms in early or mild HD. Their conclusions contradict our speculation that the grasping movement is spared because of exclusive striatal degeneration. Interestingly, Kloppel et al. (2009) reported that some cortical areas (e.g. the supplementary motor area) could compensate for dysfunction in the motor cortex (M1) in premanifest HD patients. This cortical plasticity might help to preserve digit shaping during all stages of the disease until increased cortical and striatal atrophy cause major damage to motor circuits in the brain.

Control subjects typically coordinated the independent grasping of the lips and opening of the digits to transfer the food item from the hand to the lips. In HD, the coordinated grasp by the lips and release by the digits was impaired. HD subjects placed their fingers into the mouth and closed their lips around the finger to assist release. The HD subjects may have developed this compensatory strategy because swallowing and tongue control are impaired during the course of the disease (Leopold & Kagel, 1985). The strategy may also compensate for difficulties in opening the digits to release the food, a deficit that is also reported for subjects with motor system injury (Whishaw et al., 2002). The exaggerated movement of the digits into the mouth could also be the consequence of the incapacity to terminate motion during

withdrawal of their forelimb, thus the movement would end when the fingertips cannot go further into the mouth and are stopped by the jaw. It was noted that whereas control subjects returned their head to its starting position as the hand was brought to the mouth, five of the HD subjects followed the hand with the mouth to grasp the food while three withdrew the mouth as the food approached. Thus, the mouth grasping by the HD subjects might have assisted in stabilizing the position of the head and mouth to assist food transfer.

HD subjects show deficits in posture and gait (Lalonde & Strazielle, 2007; Tian, Herdman, Zee, & Folstein, 1992) and so it is not surprising that trunk adjustments that assist the reach, although present, were affected. Mild HD subjects could adjust their upper body to counterbalance their limb weight during the reaching movement. Advancing HD was associated with leaning too far to the side or too far forward, as well as “bad” posture (i.e. slumping). Postural balance is controlled by a highly complex network of brain areas, including the cerebellum, the brainstem, the basal ganglia, the cerebral cortex, and the spinal cord (Tian et al., 1992). Because striatal GABAergic cells are the most affected in early HD, it is possible that postural control is relatively normal due to sparing of the other motor areas. As HD progresses, cell death spreads beyond the striatum into other motor areas, resulting in impaired motor function, including postural control.

Control subjects transitioned smoothly between movement elements, creating a fluid movement. Mild HD subjects were similar to control subjects in that there was little to no impairment in movement transition. In contrast, more severe HD subjects showed impairment in terminating each phase of the reaching movement, thus giving the impression that the movement element was exaggerated. In turn, the transitions

between movement elements appeared fragmented and robotic and often resulted in improper spatial location of the hand at the end of each element (i.e. moving in X, then Y, then Z direction with short pauses in between movements). Movement termination impairment was most evident at grasp, as severe HD subjects often over- or undershot the food target. It has been postulated that a dysfunctional ability to terminate movement may contribute to the degree of involuntary, choreic movements in HD (Beste, Saft, Andrich, Muller, Gold, & Falkenstein, 2007).

The HD subjects also suffer from temporal deficits, which may contribute to a deficient movement termination. Terminating motion is based on a functional timing capacity, i.e. arrival of the hand at the target is correctly processed and predicted. If impaired, the hand over- or under-shoots the target as terminating commands to the muscles cannot be given in time. Beste and colleagues (2007), who had HD subjects respond to different visual stimuli on a computer screen, observed a decline in timing function in that the higher the demands on the motor system were, the worse the performance was. 'Timing' is thought to be processed in a network of striatal medium spiny neurons (MSNs), the dopamine system and the supplementary motor area (Bartenstein et al., 1997; Macar, Coull, & Vidal, 2006; Matell & Meck, 2004; Rosas, Feigin, & Hersch, 2004). MSNs play a central role in weighting timing information from cortical and dopaminergic areas, and, as neurodegeneration occurs in striatal MSNs, even in premanifest and early stages of HD, the capacity to integrate motor and timing information might be deficient for both (Beste et al., 2007).

Visual monitoring of the reach was also impaired in HD subjects. Control subjects visually engage the target at the moment that they initiate the reach and they visually disengage the target just as the digits contact the food item (de Bruin et al.,

2008). The majority of the HD subjects displayed an impairment in visually attending to the task, in that eight of the HD subjects visually attended to the target for an extended period of time prior to movement initiation and seven of the HD subjects remained visually fixated on the food item during the entire withdrawal phase. Interestingly, there was no correlation between scores on the UHDRS and visual feedback strategy, suggesting disease severity is not the sole predictor of visual feedback strategy. As our observations conflict with results from studies exclusively testing eye movements (Lasker & Zee, 1997; Rub et al., 2009), further investigations into eye movement control during skilled reaching in a real-world task are needed to understand sensorimotor impairments and oculomotor deficits in HD.

It might be considered that the reaching analysis is redundant and might only reflect disease condition as identified by UHDRS scores. There was no correlation between the UHDRS scores and the total movement component score (data not shown), however. There are a number of possible reasons for this. First, the UHDRS was developed to give an overall score of disease stage, including cognitive function, behavioral abnormalities, functional capacity and motor function. Context specific motor behavior, such as reaching-to-eat, is not directly measured. Second, the movement element rating scale analyzes the quality of different movement components (orient, advance, grasp, withdrawal, release). The normal execution of those components results in a smooth sequencing of movements. Detailed information of hand location in space, an efficient endpoint error correction (Beste, Saft, Andrich, Gold, & Falkenstein, 2006), and an ability to terminate movement are essential. This requires a high degree of skillfulness and of motor coordination, which makes the reach-to-eat paradigm more sensitive to any changes in any level of motor control than does the UHDRS. It is interesting that there is a similar lack of correlation

between the severity of Parkinson's disease and scores on the reach-to-eat scale as subjects first presenting with Parkinson's disease display almost severe impairments as assessed by the reaching scale (Doan, Melvin, Whishaw, & Suchowersky, 2008; Sacrey et al., 2009). It would be interesting to make a similar examination of reach-to-eat movements in early onset HD subjects, because it is possible that a loss of the rotatory movements of the limb and proximal compensation are amongst the earliest symptoms of the disease. Choreatic movements may manifest in later stages of the disease, which further disrupts the coordination of a reaching movement.

In conclusion, this is the first description of the impairments in limb use for eating associated with Huntington's disease. The motor deficits are characterized by an overall jerkiness, a significant impairment in end point error correction (no smooth trajectories), deficits in timing and terminating motion (overshooting at target), motor impairments of hand rotation, and compensation with more proximal parts of the arm (movements of the elbow and shoulder). The movement rating scale described in this study is an easy and inexpensive way to quantify qualitative aspects of skilled limb movements. It can be given in any setting; it very closely models a real-world task, and can be quickly administered along with other motor and cognitive tests. The video record of the reaching movement can also be subject to more extensive biomechanical analysis using the methods developed by the present analysis. Although there were a number of commonalities in the deficits displayed by the HD subjects, performance was also variable. In future work it would be interesting to examine whether the variability is due to individual differences in the progress of the disease. Such studies could examine the progression of deficits in a longitudinal analysis and by correlating impairments with neural changes as exemplified with brain imaging. Finally, it would be important to apply our new movement analysis to

HD subjects following innovative treatment such as neurotransplantation or to pre-symptomatic HD subjects, which, according to the UHDRS, are yet to show motor impairment.

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Chapter 6

Discussion

“What is the weakest link in the analysis of behavior? In my opinion, the weakest link lies at present in the pure description of behavior.”

Philip Teitelbaum, 1994

Forelimb movements include the ability to reach for objects, shape the digits appropriately to grasp objects, and manipulate objects. Amongst these movements, reach-to-eat, the act of reaching for a food item to grasp and bring to the mouth for eating, is a natural, functional, and routinely used movement. Skilled reaching is displayed by many species of vertebrates in almost all phylogenetic orders (Iwaniuk & Whishaw, 2000). Skilled reaching is also the predominant form of reaching in early human infancy, suggesting that feeding is prioritized at this stage of development (Foroud, 2008). The centrality of skilled reaching in many different animal species not only suggests a phylogenetic commonality, but also recommends the behavior as a test of motor function in preclinical animal studies (Gharbawie, Karl, & Whishaw, 2007; Moon, Alaverdashvili, Cross, & Whishaw, 2009) and for human neurological assessment (Doan, Melvin, Whishaw, & Suchowersky, 2008; Klein, Sacrey, Dunnett, Whishaw, & Nikkhah, 2011; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002). Comparative and functional studies of skilled reaching are aided by the fact that the movements, and their sensory attention, are readily subjected to experimental analysis in the laboratory (Bishop, 1964; Bonfiglioli, De Berti, Nichelli, Nicoletti, & Castiello, 1998; Mackenzie & Iberall, 1994; Marotta, Medendorp, & Crawford, 2003; Sacrey, Clark, & Whishaw, 2009; Whishaw & Pellis, 1990; Whishaw, Pellis, & Gorny, 1992). The purpose of the present chapter is to describe the sensory attention of skilled reaching, and in so doing, the paper draws heavily from observational studies on nonhuman animals, developing human infants, and human subjects with

neurological conditions. Thus, the methods derive in many ways from the behavioural methods pioneered by Philip Teitelbaum (Teitelbaum, 1994).

The early phylogenetic appearance of skilled reaching in terrestrial vertebrates and its widespread manifestation in different animal orders might suggest that it is a single motor action or synergy. Analysis of the movement, however, shows that it is a composite action with many movement elements or primitives that include orienting the eye, head, and hand, grasping the target food item, withdrawing the food to the mouth, releasing the food into the mouth, and returning the hand to its starting position. There is a paucity of information related to the phylogenetic evolution of the various elements that comprise skilled reaching movements, but Gray (Gray, O'Reilly, & Nishikawa, 1997) has described a number of forelimb movements used in prey handling by frogs. These movements include advancing a limb and grasping prey, bringing it to the mouth, and wiping, in which the palm pushes protruding prey toward the midline of the mouth. It is likely that each of these movement elements has its own phylogenetic history, with the elements expressed and combined in somewhat different ways in different animal species. Human skilled reaching appears mainly to feature the first two of these movements.

The sensory attention of skilled reaching movements is also phylogenetically heterogeneous. This is exemplified by differences between the sister clades of rodents and primates. For example, the rat identifies distal reaching targets using olfactory and tactile information (Whishaw & Tomie, 1989). If a rat is blindfolded, its food detection and reaching are unaffected, but if its olfactory bulbs are damaged, it reaches as if blind. The rat will also reach to take objects from its mouth to hold them

for eating (Whishaw et al., 1992). This movement features online somatosensory guidance and, because the rat shapes its digits appropriately to object size, this guidance includes information from perioral receptors about the size and shape of the food object. By contrast, primate hand transport is guided by vision and withdrawal by somatosensation (Jeannerod, 1984; 1988; 1999). The evolution of a dual control of hand guidance in primates is accompanied by major changes in the sensory attention of the motor system in primates relative to that of rodents (Whishaw, 2003).

Furthermore, the visual attention of hand movement in primates is hypothesized to be influenced by the properties of the target object. Reaching can be guided by the external properties of an object, such as its shape and size, or by other perceptual properties of an object (Milner & Goodale, 2006). Online guidance is proposed to be mediated by a dorsally located visual pathway that projects through the parietal lobe, the dorsal stream, while object recognition is mediated by a ventrally located pathway that projects through the temporal lobes, the ventral stream (Goodale, Meenan, Bulthoff, Nicolle, Murphy, & Racicot, 1994; Goodale & Milner, 1992).

In its overall structure, skilled reaching combines a hand movement directed toward grasping an external target, followed by a hand movement directed toward the body to place the food in the mouth. Both movements display a similar level of arm and hand dexterity. Jeannerod (1986) documents the dependence on vision for digit shaping that anticipates grasping a distal object. Edwards et al., (Edwards, Wing, Stevens, & Humphreys, 2005) report that hand movements, including grasping movements, directed toward the body without visual guidance are perhaps more accurate than visually guided movements to distal targets. For example, grasping the

nose and mouth features appropriate hand pre-shaping and grasping. Karl et al. (Karl, Sacrey, Doan, & Whishaw, 2012) also show that, in the absence of vision, the hand is accurately shaped to take food items from the mouth. Together, these studies suggest that skilled reaching is mediated by at least two different types of sensory attention or sensory reference frames, vision to guide the hand to a distal target and somatosensation to grasp the target and transport it to the mouth for release.

The claim that two sensory attention systems control skilled reaching raises the questions of how they are coupled in mature adults, how coupling develops in infancy, and how coupling is influenced by neurological disorders. The first part of this paper describes the coupling of vision to advancing the hand towards a target and pre-shaping the digits to grasp, and the coupling of somatosensation to grasping the target, withdrawing the hand to the mouth, and releasing the food item into the mouth. The second part of this paper describes the development of the relationship between vision and somatosensation and skilled reaching in maturing human infants. The third part of this paper describes changes in the relationship between visual and somatosensory attention in neurodegenerative disease. The thrust of the studies suggests that the sensory attention of skilled reaching is organized, but also plastic, in that the adult pattern is acquired through experience and can be modified to compensate for the impairments imposed by neurological disorders.

Visual Engagement and Disengagement with Hand Advance

The skilled reaching task developed by Whishaw and colleagues for human subjects is illustrated in Figure 1. A subject sits comfortably in a chair and is asked to reach for a CheerioTM that has just been placed on a pedestal in front of her/him. CheeriosTM are used as a reaching target because they are small and will dissolve in the mouth and so can be eaten by normal subjects, children, or subjects with neurological conditions. The subjects are given no special instructions except that they are to place their open hands on their lap and, once the food is placed on the pedestal, to reach for it and eat it. Biomechanical markers on the reaching arm track the arm's movement, and eye-tracking glasses or visual occlusion goggles are worn to allow or occlude vision. Movements of the hand and eyes are digitized offline in order to describe the temporal relationship between the arm and eye movements (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008).

The record of eye and hand movements during skilled reaching reveal a close temporal relationship between visual attention and hand advance. As is illustrated in Figure 2, a subject does not look at or near the pedestal or food item prior to the start of forelimb movement, but instead, looks at the experimenter or looks around the test room. Nevertheless, immediately prior to, or concurrent with, the first hand movement, a subject visually fixates the food item and maintains visual attention as the hand is lifted from the lap, the digits are collected (lightly closed and flexed), the hand is advanced towards the target, and the digits pre-shape for grasping. Just as tactile contact with the food item is made however, the eyes disengage, usually with a blink and an upward glance. Consequently, subjects are looking elsewhere as the hand

grasps the target, withdraws the food item to the mouth, releases the food into the mouth, and is replaced on the lap at the end of the trial (de Bruin et al., 2008).

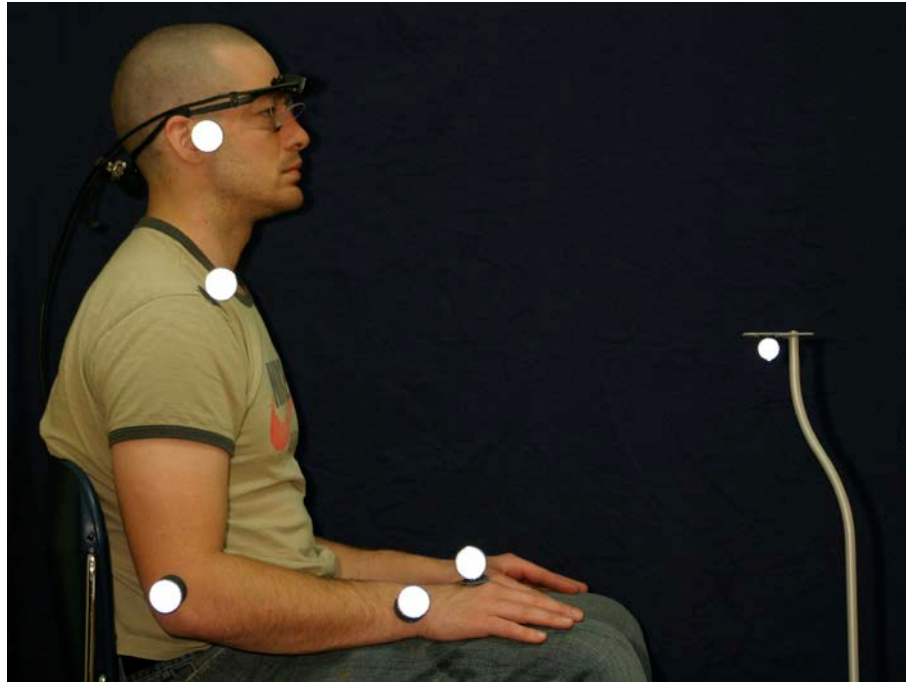


Figure 1. A subject sits before a pedestal on which a food item is placed. Food is placed on the pedestal and the subject begins the first reach with hand open on the lap. The white dots represent light reflective markers on the subject (left) and the food target (right). The headset is for eye-tracking. Figure taken from (Sacrey et al., 2009) with permission.

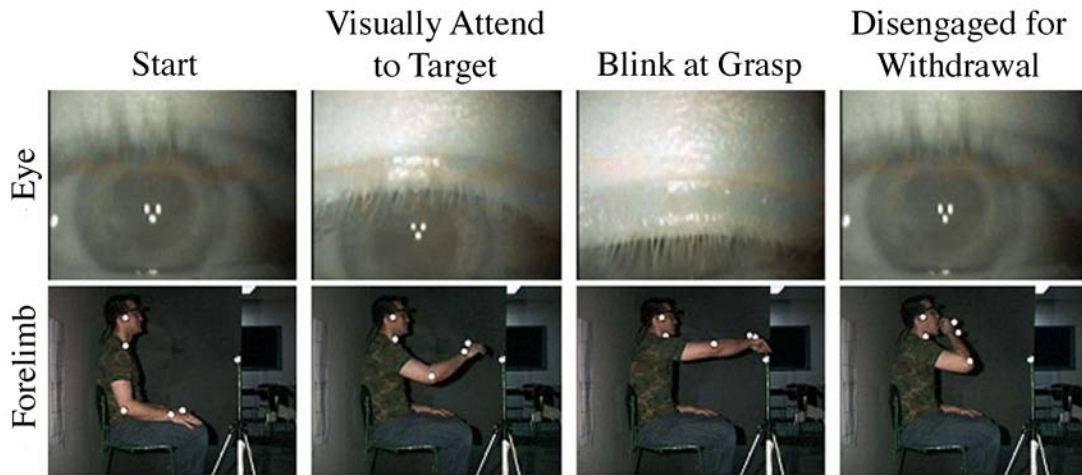


Figure 2. Eye movements and forelimb movements during the reach-to-eat task. Start: gaze is not directed to the target and the hand is in the resting posture. Visually attend to target: the eyes fixate the food item as the hand is advanced towards the target. Blink at grasp: gaze disengages, usually with a blink, as the food item is contacted by the digits. Disengaged for withdrawal: the eyes remain disengaged from the food item as the hand is withdrawn to the mouth. Figure adapted from de Bruin et al., 2008.

It is interesting to note that visual disengagement from the target food item and hand is associated with a blink on about two thirds of all trials and is also associated with a large deviation of the eyes away from the target. Elsewhere, it is reported that gaze shifts are accompanied by blinking (Evinger, Manning, & Sibony, 1991), that the eyes reorient within 60 to 70% of a blink (Rottach, Das, Wohlgemuth, Zivotofsky, & Leigh, 1998), and that the probability of a blink occurring is proportional to the size of the gaze shift (Evinger et al., 1991; Watanabe, Fujita, & Goyoba, 1980).

Thus, both visual fixation with the target and visual disengagement from the target are associated with distinct head and eye movements. This pattern of movement results in a brief period of visual attention to the target that is temporally coupled with advance of the hand to the target and then a redirection of visual attention away from

the target as the target is grasped. The economical temporal coupling of visual attention with hand advance to the target ensures appropriate hand direction and shaping to grasp the target.

Directing gaze to some other object in the room as the target is grasped may reduce attentional interference between vision and the somatosensory attention of grasping, withdrawal, and release of the food into the mouth. Redirecting gaze may also provide a visual anchor to stabilize posture for the target capturing movements (Clement, Pozzo, & Berthoz, 1988; Paillard & Amblard, 1985), may allow a subject to search for the next food item, and may even signal the experimenter a readiness for subsequent trials (de Bruin et al., 2008). Visual redirection may also facilitate somatosensory attentional processes related to the capture and withdrawal of the target. These movements involve sequential regulation of the forces with which the digits grasp the food (Harada et al., 2004; Mackenzie et al., 1994; Rothwell, Traub, Day, Obeso, Thomas, & Marsden, 1982), accurate targeting of the mouth, and the adjustments of the digits to release the food as it contacts the lips.

To test the idea that visual engagement is specifically associated with hand advance versus hand withdrawal, de Bruin and colleagues (de Bruin et al., 2008) fitted subjects with visual occlusion goggles that were electronically controlled to occlude vision from the moment that the reach movement is initiated to the point that the hand is replaced on the lap at the end of the trial. The goggles also block peripheral vision, which may be sufficient to guide that hand to the mouth (Danckert & Goodale, 2001; Previc, 1990; Whishaw, 1994). Kinematic measures and qualitative description of arm and hand movements indicated that advancing the hand and hand

shaping are disrupted by visual occlusion. As illustrated by the latency measurements shown in Figure 3, advancing of the hand towards the target is slowed. In addition, the hand overshoots or undershoots the target, and the digits do not pre-shape accurately for grasping (Chieffi & Gentilucci, 1993; Churchill, Hopkins, Ronnqvist, & Vogt, 2000; de Bruin et al., 2008; Fourkas, Marteniuk, & Khan, 2003; Jackson, Jones, Newport, & Pritchard, 1997). Once the food item is contacted by the ventral surface of the digits or palm however, the remaining movement components are similar to those of the sighted condition. Movement speed is normal, as are the time and accuracy of moving the hand to the mouth, release of the food into the mouth, and replacing the hand at its starting position. Thus, visual occlusion disrupts hand advance and hand shaping but does not affect food grasping, hand withdrawal, or release of the food into the mouth (de Bruin et al., 2008).

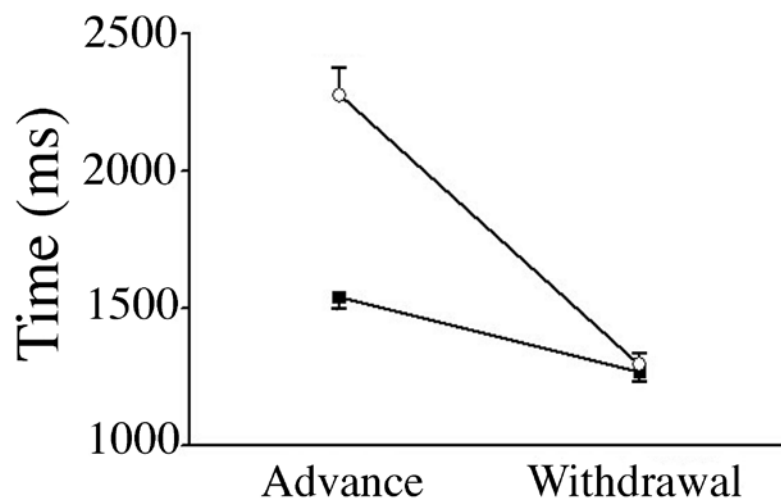


Figure 3. Mean and standard error for time to complete advance and withdrawal movements when vision is allowed (black squares) and when vision is occluded (white circles). Note the increase in time to reach for and contact a food item when vision is occluded versus equivalent withdrawal times in the vision and occluded conditions. Figure taken from de Bruin et al., 2008 with permission.

The evidence that visual attention of the food target is closely coupled to the events associated with hand advance but not hand withdrawal and that visual occlusion disrupts the events related to hand advance but not the events related with hand withdrawal, supports the idea that skilled reaching is controlled by at least two different attention subsystems. That vision is associated with hand advance is consistent with many previous studies (Carlton, 1981; Foroud & Whishaw, 2006; Prablanc, Echallier, Komolis, & Jeannerod, 1979; Snyder, Carlton, Dickinson, & Lawrence, 2002; von Donkelaar, Siu, & Waltarschied, 2004; Whishaw et al., 2002). Visual attention likely identifies the location of the food item, its size, and its shape (Berthier, Clifton, Gullapalli, McCall, & Robin, 1996; Mackenzie et al., 1994; Snyder et al., 2002; Wong & Whishaw, 2004) and so directs the hand appropriately (Gharbawie, Stepniewska, & Kaas, 2011; Goodale et al., 1992; Goodale et al., 1994; Smeets & Brenner, 1999). Visual disengagement at tactile contact may re-prioritize attention, enhancing somatosensory awareness of the food item for appropriate grasping (Harada et al., 2004; Mackenzie et al., 1994; Rothwell et al., 1982), withdrawal accuracy, and food release into the mouth (de Bruin et al., 2008).

At present, the details of sensory attention of the withdrawal phase of reaching are not well described, but it is likely that both hapsis and proprioception are involved. Hapsis likely confirms handgrip position and regulates forces for grasping food and for releasing it to the mouth (Gordon, 1994; Winges & Santello, 2005), whereas proprioception likely mediates the movement of the hand relative to the mouth (Maravita, Spence, & Iberall, 2003). Future studies could investigate which of the many components of the somatosensory system are associated with the withdrawal phase of the reach-to-eat movement. For example, the role of joint and

tendon receptors, proprioceptive signals from muscle spindles, and skin receptors could be perturbed to examine their contributions to the withdrawal response.

The Development of the Visual Attention of Skilled Reaching

Skilled reaching is a dominant form of targeted reaching in infants during the first year of life. Beginning with the first attempted grasps of movable objects, infants always attempt to place an object that they have grasped into their mouth (Foroud, 2008; Piaget, 1952). Even on occasions in which they play with a grasped object or move it from hand to hand, it is first brought to the mouth. The feeding-related use of the hands is featured early in life in grasping a breast during suckling and grasping a bottle at feeding. Thereafter, infant skilled reaching and its sensory control mature gradually to an adult pattern.

During the first month of life, infants frequently hold their hand in a fist position (Sacrey & Whishaw, 2010), but as noted above, they will grasp objects such as a breast or bottle when feeding. During the first to fifth months of life, infants display many hand movements that are associated with independent digit movements, which have been described as hand babbling (Wallace & Whishaw, 2003). They then engage in self-grasping, but make few successful reaching movements towards distal objects (Ennouri & Bloch, 1996; von Hofsten, 1982; Wallace et al., 2003). After five months of age, infants reach for objects bimanually, using shoulder and torso movements, with little hand shaping (Foroud, 2008; Touwen, 1976; White, Castle, & Held, 1964). From 10 months onward, they develop directed reaching using only one hand, and they begin to display directed hand shaping to purchase large objects with a

whole hand grasp and small objects with a pincer grasp (Touwen, 1976; White et al., 1964). Because reaching at ages 6 months to one-year features movements to distal targets, these ages were included in the present thesis to describe the development of the visual attention of reaching.

The skilled reaching task for human infant subjects is illustrated in Figure 4. Eight infants were filmed between 6-months of age to one-year of age as they engaged in reaching acts. From six-to-nine months of age, the infant were seated in a head and torso supportive chair that allowed the arms and hands freedom to reach for small toys held in front of them at arms length by a parent. Nine-and-a-half-to-twelve-month-old infants were seated in a high chair with an attached food tray and they

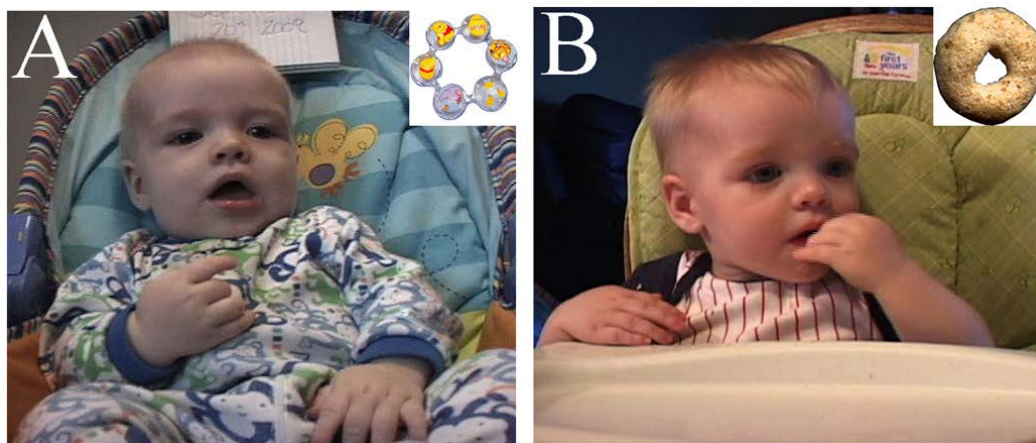


Figure 4. Experimental set-up for infants. A) Six-to-nine-month-old infants are seated in a back and neck supportive chair with their hands and arms free to grasp small toys (insert) their parent holds in front of them at arms length. B) Nine and a half to twelve-month-old infants are seated in a high chair with an attached tray. A food item (insert) is placed on the food tray for the infant to grasp and withdrawal to the mouth.

reached for Cheerios™ that were placed on the tray. The details of arm movements and eye movements were acquired from the video record and analyzed frame-by-frame using digitizing software. The temporal coupling of eye movements and hand movements were summarized month by month.

As is illustrated in Figure 5, there is progressive development in visual fixation and disengagement in the developing infants until visual attention of reaching takes an adult form at about one year of age. Six-month-old infants (Figure 5, top) visually fixate a target for an extended duration prior to making unrefined and jerky hand movements with little hand shaping. They also continue to visually attend the target after it is grasped and while it is being brought to the mouth. As shown in Figure 6, the accuracy with which the object is brought to the mouth is poor in six-month-old infants, with the object usually first contacting the chin or cheek on its way to its final destination. By nine months of age, hand trajectories become smoother, and digit shaping to the target is present. The infants also direct their eyes to the target just before initiating hand advance. They still do not visually disengage the target as it is grasped, however. Only by twelve months of age do infants (Figure 5 bottom) visually attend the target during the reach and then visually disengage the target as soon as it is contacted with the digits.

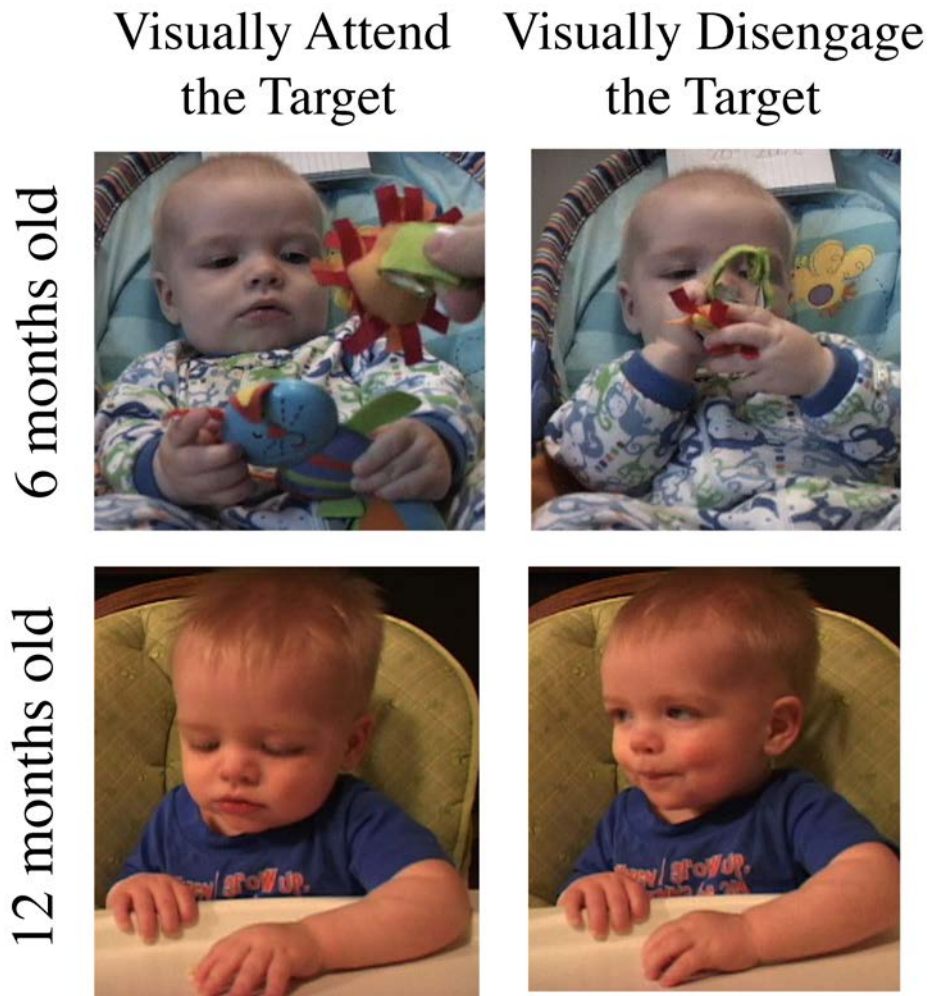


Figure 5. Events of visual fixation (left) and visual disengagement (right) for six-month-old (top) and twelve-month-old (bottom) infants. Six-month-old infants visually fixate on a target for an extended duration of time prior to moving their hand towards the target and continue to fixate the target as it is brought to the mouth. Twelve-month-old infants visually fixate on a target immediately prior to moving their hand towards the target and visually disengage from the target as it is contacted by the hand. Pictorial representations based on averages of 8 infants followed longitudinally from 6-months-old to 12-months-old.



Figure 6. Pictorial representations of the point of first contact of the target on the face for six, nine-, and 12-month-old infants. Each colour represents a different infant. Note: 6-month-old infants first contact the chin or cheek before placing the target into the mouth. By 12-months-old, infants accurately place the target into the mouth. Data is a pictorial representation of 8 infants followed longitudinally from 6-months-old to 12-months-old.

Figure 7 illustrates durations of visual attention on a target prior to reach initiation (top) and following object grasping (bottom) for results collected in 6-, 9- and 12-month-old infants. It is interesting that the narrowing of visual attention to initiation of the advance movement is present by 9 months of age, whereas disengagement matures somewhat more slowly and is not mature until about 12 months of age. These findings are consistent with reports that concurrent hand-eye movements are observed in infants as early as two- to three-months of age (Brunner & Koslowski, 1972; White et al., 1964) and that vision contributes to somatosensory attention (Hein & Diamond, 1972; Held & Bauer, 1974; McCarty, Clifton, Ashmead, Lee, & Goubet, 2001), but the results also illustrate that there is a prolonged period of maturation of visually-guided hand movements. It is noteworthy that the maturation of visual attention of the hand to the target is paralleled by maturation of the withdrawal movement (present thesis). Guidance of a grasped object to the mouth is initially inaccurate and misses the mouth and then becomes more accurate with maturation (see Figure 6).

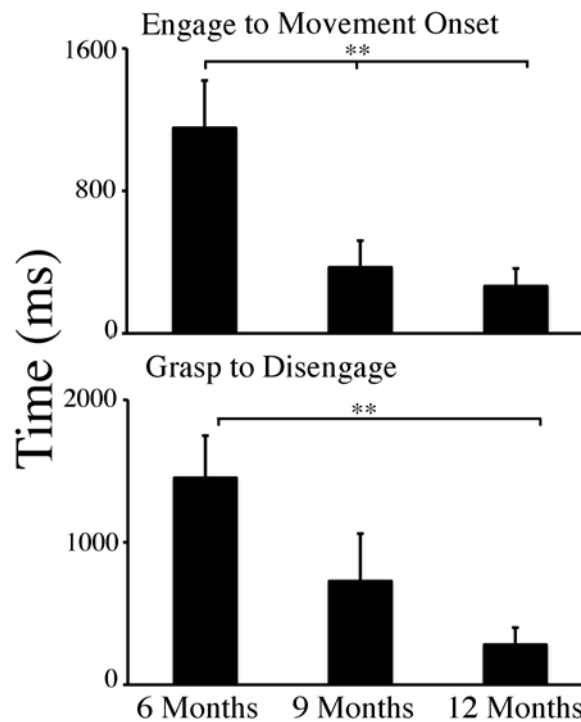


Figure 7. Time (mean and standard error in milliseconds) for six-, nine-, and twelve-month-old infants to move their hand following visually engaging a target (top) and duration of time to visually disengage from target following grasp (bottom). Note: the adult relationship of engage to move develops more abruptly than the adult pattern of grasp to disengage. Data is averages of 8 infants followed longitudinally from 6-months-old to 12-months-old.

From six months of age to twelve months of age, the movements of hand shaping and the rotatory movements of the hand also becomes more mature. Hand trajectories become more direct, digit shaping becomes appropriate to the target, and the target is brought accurately to the mouth. A summarization of the changes in movement quality from six-, nine-, and twelve-months-old is illustrated in Figure 8 (the lower the score, the better the quality of movement).

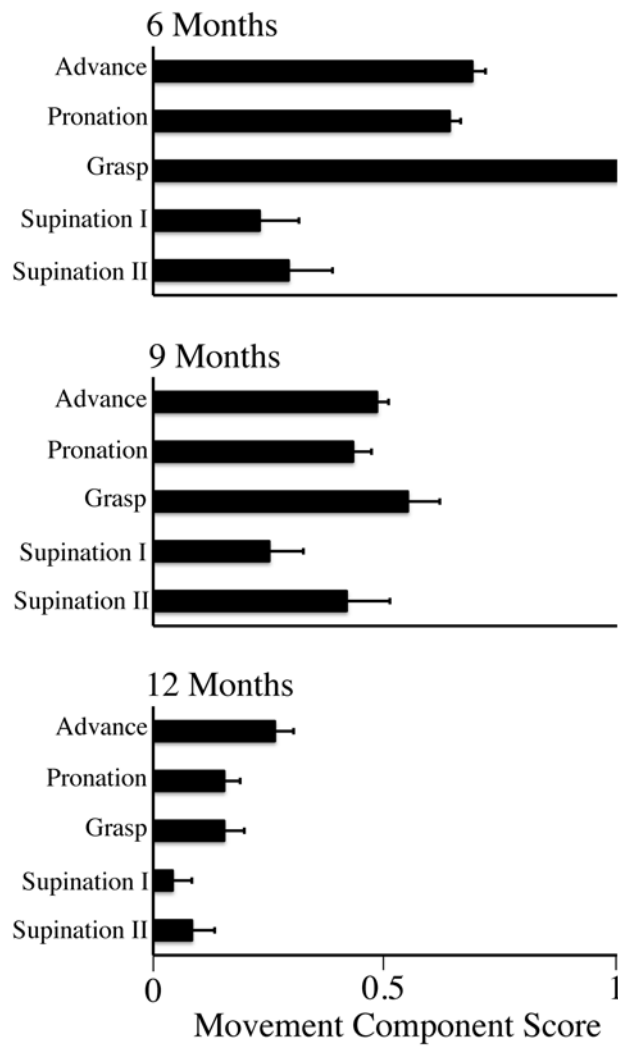


Figure 8. Movement component score (average and standard error) for six-, nine-, and twelve-month-old infants. A score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent. Data is averages of 8 infants followed longitudinally from 6-months-old to 12-months-old.

Thus, the maturation of skilled reaching movements is associated with restriction of visual attention to hand advance and of somatosensory guidance to hand withdrawal. It is interesting that monkeys reared with normal vision but without sight of their forelimbs are retarded in the development of functional forelimb movements,

but when vision is returned, forelimb movement control quickly improves (Held et al., 1974).

One can speculate on why the earlier stages of infant reaching are associated with exaggerated visual attention both prior to and following a grasp. Prolonged visual attention may be associated with learning about objects and in monitoring the objects, to ensure proper finger placement, and to learn about the association of the grasped object and the grasping hand. Grasp kinematics in infants are associated with variable force-rate peaks and in re-posturing of the digits before a stable grasp is achieved (Catherwood, 1993; Forssberg, Eliasson, Kinoshita, Johansson, & Westling, 1991). The endpoint errors made by young infants in bringing an object to the mouth further supports the idea the somatosensory attention of withdrawal takes time/experience to develop. As noted above, there is evidence that somatosensory attention of purposeful hand movement is aided by visual observation of the limb (Hein et al., 1972; Held et al., 1974; McCarty et al., 2001; Warren, 1984). While the infants are visually attending their hands and the grasped object as they bring it toward the mouth, they are likely acquiring somatosensory sophistication.

Abnormalities in the Visual Attention of Skilled Reaching in Pathological Diseases of the Motor System

Neurodegenerative diseases of the motor system are characterized by gradual disruption to motor control and execution. Skilled reaching impairments have been described for two neurodegenerative diseases, Parkinson's disease (PD) and

Huntington's disease (HD). In these conditions, the movement impairments share similarities but also feature differences (Klein et al., 2011; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Sacrey et al., 2009, Sacrey, Travis, & Whishaw, 2010).

Both diseases are characterized by progressive changes in hand movements, in that there is little rotation of the hand, digits are shaped at an abnormal temporal location, either too soon or too late, and the food item is released with difficulty into the mouth. Other movement differences include slowness of movement in the PD subjects and many discontinuities in advance and withdrawal movements in the HD subjects (Doan et al., 2008; Klein et al., 2011; Sacrey et al., 2009; Sacrey et al., 2011; Whishaw et al., 2002).

In both conditions, reaching impairments are amongst the earliest presenting symptoms and the impairments get worse with disease progression, as assessed by independent rating scales of movement (Hoehn & Yahr, 1967; Huntington Study Group, 1996). In both conditions, there are many individual differences in symptoms and these individual differences are likely related to differences in the neural structures affected by the disease condition at the time of testing. In addition, for both conditions, the movement impairments are minimally improved by pharmacology and other therapies.

Using the reach-to-eat task, it is found that, in addition to the motor impairments, there are also changes in sensory attention related to the reaching movements for both PD and HD (Klein et al., 2011; Melvin et al., 2005; Sacrey et al.,

2009; Sacrey et al., 2011). Unmedicated PD subjects first presenting with Parkinsonian symptoms visually fixate the food target with the commencement of hand advance but they then continue to visually attend the target/hand during grasping (Melvin et al., 2005). With disease progression, subjects begin to visually fixate the target well before the initiation of hand advance and then continue to visually attend the hand for a longer period during grasping and during withdrawal (Sacrey et al., 2009; Sacrey et al., 2011). As displayed in Figure 9, medicated subjects with severe Parkinsonian symptoms may stare at the food target location well before the food is placed there and then only disengage that location as they visually follow the hand as it is withdrawn to the mouth. Similarly, HD subjects may visually attend a target for an extended period of time prior to the onset of forelimb movement and they may continue to attend the hand during grasping and during the first part of the withdrawal. Many Huntington's subjects also visually disengage and then reengage the target during hand advance and hand withdrawal (Klein et al., 2011).

Although impairments in movement associated with skilled reaching in PD are not improved by L-dopa medication, Sacrey and colleagues found improvements in visual attention (Sacrey et al., 2009; Sacrey et al., 2011). Visual attention is normalized in less severe PD subjects and improved in more severe PD subjects by L-dopa medication (Sacrey et al., 2009). In addition, music therapy is also beneficial in normalizing the relation between visual attention and skilled reaching. Listening to preferred music through headphones, although not improving the movements in PD, does normalize visual attention in unmedicated PD subjects (Sacrey et al., 2011), and, when combined with L-dopa medication, improves visual attention even in severe PD subjects (Sacrey et al., 2009).

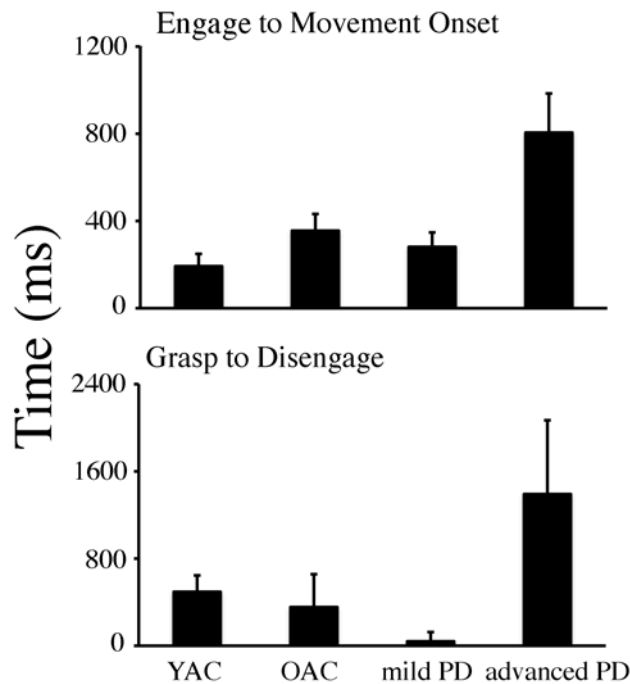


Figure 9. Time (mean and standard error in milliseconds) for young adult controls (YAC), old adult control (OAC), medicated mild PD subjects, and medicated advanced PD subjects to move their hand following visually engaging a target (top) and duration of time to visually disengage from target following grasp (bottom). Note: advanced PD subjects stare at the target before initiating a reach movement and continue to stare at the target after it is grasped. Data is averages of 8 subjects in each group.

The prolonged visual attention demonstrated by the unmedicated mild PD subjects may have a number of causes. First, one of the cardinal features of PD is bradykinesia (Parkinson, 2002; Pheiffer, Ebadi, & Wszolek, 2011). Accordingly, a general slowing of movement may be responsible for prolonged gazing at a target. Second, the prolonged visual attention on the food item may be a compensatory mechanism to supplant the impaired somatosensory guidance of the reaching limb (Flowers, 1976; Sacrey et al., 2009; Schettino, Adamovich, Hening, Tunik, Sage, & Poizner, 2006). Changes to somatosensory function have also been reported for HD (Albin & Young, 1988). Smith et al (Smith, Brandt, & Shadmehr, 2000) show that

HD subjects are impaired in error correction during voluntary movements, and suggest that this impairment is due to deficient somatosensory feedback. It is of interest that the pattern of visual attention used during the reach-to-eat task is not correlated with disease severity, as assessed by the Unified Huntington's Disease Rating Scale (Klein et al., 2011).

There are several possible explanations for why music normalizes sensory attention. There is evidence that music improves dopaminergic transmission (Blood & Zattore, 2001; Menon & levitin, 2005; Pankseep & Bernatzky, 2002; Sutoo & Aklyama, 2004), suggesting that music and medication would have similar positive effects through a direct effect on the mechanisms associated with dopamine release. Music has also been found to elicit increases in cerebral blood flow to the ventral striatum, amongst other brain structures (Blood et al., 2001). Through this action, music may have a general arousing effect. Finally, it has been proposed that music may activate a nonspecific auditory arousal system, which in turn facilitates motor performance (Chomiak, Peters, & Hu, 2008; Hu, 2003). Accordingly, the effects of music and dopamine medication may exert beneficial effects through different mechanisms and thus may be additive (Sacrey et al., 2009). Future studies could investigate the role of preferred music on HD to determine any beneficial effects of music on movement components or sensory attention of reaching-to-eat in HD.

Skilled reaching is a phylogenetically ancestral act, the earliest hand movement to develop, and the most frequently used movement in daily activities. It is an act that contributes to efficiency in food competition, aids in the exploitation of novel food resources, and is an ancestral act for the evolution of other forms of hand movement. Nevertheless, the movement is complex and consists of many rotational alterations and hand shapes. Movement accuracy also depends upon different frames of sensory attention; first to capture objects in extra-personal space and then to deliver them into personal space and to release them into the mouth. It is not surprising, therefore, that the movement is associated with precision and economy in sensory attention.

Three lines of evidence presented in this thesis suggest that visual attention is closely associated with hand advance and digit shaping, while somatosensory attention is associated with grasping, withdrawal, placing the food into the mouth, and in returning the hand to its starting position. First, in normal subjects, visual attention on the target is closely coupled to hand advance, with visual disengagement occurring as the digits touch the target (de Bruin et al., 2008). Second, this coupling develops slowly in young infants, with visual attention first occurring well before reaching movements are initiated and continuing during grasping and as an object is withdrawn to the mouth. Only by about one year of age does the close coupling of visual attention to hand advance mature (present thesis). Third, the close coupling of vision to hand advancement can dissolve in neurological disease. In the conditions of Parkinson's disease and Huntington's disease, there are disturbances of attention with visual attention occurring before the reach and continuing after grasping (Klein et al., 2011; Sacrey et al., 2009; Sacrey et al., 2011).

The same three lines of evidence suggest that somatosensory attention controls the events associated with grasping and hand withdrawal. Nevertheless, the relationship of somatosensory attention to movement control may be different in a number of ways from that of visual attention. Somatosensory attention may mature more slowly than visual attention in infants. This suggestion stems from the observation that, although infants quickly develop visual orienting to graspable objects, they display a prolonged phase in which they watch the grasping of an object as it is withdrawn toward the mouth. Furthermore, infants are surprisingly inaccurate in bringing an object to their mouth once it is grasped (present thesis). Somatosensory attention may be impaired earlier than visual attention in PD and HD. For example, advanced PD subjects display exaggerated visual attention prior to the beginning of hand advance, during grasping, and during hand withdrawal, perhaps to compensate for somatosensory inattention (Klein et al., 2011; Sacrey et al., 2009; Sacrey et al., 2011).

Jeannerod (1986) has proposed a model of skilled reaching in which visual and proprioceptive maps co-equally direct reaching to a target. The model is based in part on findings that show that damage to both visual and somatosensory regions of the neocortex impair hand advance. The finding reviewed in the present thesis suggest that there is a higher level of attentional control of skilled reaching, in which visual attention is coupled to hand advance towards a target and somatosensory attention is coupled to withdrawal of the target to the mouth.

The different attention processes may be properties of cortical networks associated with limb advance and withdrawal respectively. Electrophysiological and brain imaging studies of humans suggest that the dorsal premotor cortex moves the hand to an external spatial target, whereas the ventral premotor cortex moves the hand to the mouth (Graziano, 2006; Graziano, Aflalo, & Cooke, 2005). Dorsal premotor cortex is a component of the visual dorsal stream (Milner et al., 2006), whereas ventral motor cortex is a component of the somatosensory dorsal stream (Fang, Stepiewska, & Kaas, 2005; Gharbawie et al., 2011). Magnetic resonance imaging shows that these transcortical pathways mature at the time that the adult-form of visual/somatosensory guidance of hand movements matures in infants (Paus, Collins, Evans, Leonard, Pike, & Zijdenbos, 2001). Functional MRI illustrates differences in activation of these neural regions in visually guided movement and proprioceptively guided movement respectively (Bernier & Grafton, 2010).

The evidence reviewed here that skilled reaching is mediated by two different attention systems provides other insights into the function the dorsal and ventral streams (Milner et al., 2006). It is possible that in the early stage of development, in which infants display exaggerated visual guidance of reaching and rather poor accuracy, the ventral stream mediates the movement. This is a stage in which the infant is learning about the many extrinsic properties of objects including their texture, pliability and edibility. This object knowledge is likely a function of temporal lobe memory systems (Goodale et al., 1992; Goodale et al., 1994). In turn, dorsal stream hand guidance develops secondarily to ventral stream hand guidance, and by exclusion, responds to intrinsic properties of objects such as size and shape (Goodale et al., 1992; Goodale et al., 1994). The appearance of exaggerated visual guidance of

hand movements in PD and HD suggest that the perception and response to the intrinsic properties of objects is more affected in these conditions and that ventral stream visual processes compensate.

It is interesting to speculate that the coupling of sensory attention featured in skilled reaching may be featured in other movements. For example, walking requires alternating visual attention on distal objects and somatosensory attention of moment-to-moment stepping movements. Visual attention is directed to the terrain a few steps in advance of a present position, and then a step is mediated by somatosensation when the immediate target of a step is not in view (Mohagheghi, Moraes, & Ptla, 2004; Ptla & Vickers, 1997; Ptla & Vickers, 2003). Similarly, many other movements, including dancing, operating an automobile, and handling kitchen utensils, involve alternating control by visual and somatosensory attention. Differential disruption in the control of visual and somatosensory systems could result in abnormalities in these other movements, just as they do for skilled reaching. For example, a tendency to prolong visual fixation on a visual feature during walking would likely impair the smooth flow of walking. The freezing in walking displayed by PD subjects in complex visual environments may be related to such an impairment in visual disengagement. Therapy including drug treatments and music may have a beneficial effect on eye movements, and thus could contribute to improved walking. By facilitating visual disengagement, therapy may improve performance in tasks that demand frequent shifts in sensory attention (Pacchetti, Mancini, Aglieri, Fundaro, Martignoni, & Nappi, 2000; Posner & Raichle, 1994; Slavutsakaya & Shulgovskii, 2007). It would be interesting to monitor the coupling of visual and somatosensory attention in movements other than reaching in developing infants, in adults, and in neurological disease.

Finally, the behavioural studies summarized here also suggest that associative processes of learning contribute importantly the development of sensory frames of reference associated with skilled reaching. Notably, the development of sensory attention of reaching in infants is long and, over the formative period of the first six months of life, infants must make hundreds if not thousands of reaching movements. Perhaps the learned associations involved in the division of the sensory attention of reaching are those most sensitive to neurological diseases such as Parkinson's disease and Huntington's disease. This idea may be supported by findings that activation therapy, e.g., music therapy, can improve the sensory attention of reaching in Parkinson's disease. The idea that associative learning is importantly involved in the sensory attention of skilled reaching could be further examined by using the skilled reaching task as a therapeutic instrument. Perhaps daily therapy in skilled reaching could remediate arm and hand use more generally in motor disease conditions. It would be relatively easy to include skilled reaching demands in the daily activity of patients.

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Future Directions

The tight temporal coupling of the hands and eyes of the reach-to-eat movement serves as a biomarker of typical development and healthy brain function. This movement is performed daily by individuals and relies on well-learned motor and sensory integration for completion. As such, there is much potential for use of this simple and inexpensive reach-to-eat task to determine impairments to sensation or movement.

The reach-to-eat task can be performed by children very early in development, and thus can serve as an early marker of typical development/brain injury in children at risk for autism, fetal alcohol syndrome, cerebral palsy, and concussion following sports injury, amongst others. Similarly, the reach-to-eat task serves as a useful tool to determine impairments to the sensorimotor system for adults with brain injury, as it is very quick to complete, does not require practice, and is not cognitively or motorically taxing. The movement itself is easily scored and can be used by clinicians to describe sensory and motor impairments, as well as track the progression/improvements in disease course for those affected by sensorimotor disorders.

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