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THE ORIGINS OF INDIVIDUAL DIFFERENCES IN SKILLED REACHING FOR FOOD IN RATS

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DOCTOR OF PHILOSOPHY

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DEDICATION

To my family

ABSTRACT

Rats display considerable individual differences in performance of skilled reaching for food. Such variability in the normal performance of the rats intrudes upon the interpretation of many different experimental investigations in behavioral neuroscience. Understanding the origins of individual differences in skilled reaching performance of the rat provides insights into brain function, the evolution of skilled reaching, and also it helps optimizing preventative and therapeutic care. Although variability in skilled reaching is manifested in many studies, their origins remain poorly understood. The objective of the present thesis was to document the individual differences in skilled reaching for food in rats and to examine potential sources of individual differences in brain function. The present studies revealed that the difference in reaching success displayed by rats was a robust and constant feature in different conditions, emerged with practice and the motor cortex plays an important role in such variability.

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My experience in the Whishaw laboratory led me to an understanding of science as a discipline that works through perseverance, hard work, commitment and intelligence, the elements that have been in the core of scientific enterprise since the beginning and will not change with the accumulation of knowledge or complexity of technology. Such impression was reflected in Dr. Whishaw's supervision throughout my training by walking with me toward discovering the truth or next to me encouraging an independent approach. I wish to express my sincere appreciation to Dr. Whishaw for such opportunity.

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CHAPTER 1

General Introduction

Introduction

The present thesis investigates individual differences displayed by rats in skilled reaching performance. The rat was chosen as a subject because it is widely used as a model for investigating the motor system more generally. Skilled reaching, in which a rat reaches for a food pellet with a hand, was chosen because the movement is a preplanned movement with a very variable success outcome.

The purpose of the present introduction is to first provide some of the background on the neural organization of motor control, which will be followed by a summary on individual differences in motor performance. The introduction will then describe the rat model of skilled reaching and this will be followed by a summary of the use of the rat as a model in investigating neuroplasticity in the motor system, the presumptive neural basis of individual differences in motor performance. The objectives of the thesis will be described at the end of this chapter.

Neural organization of motor control

The neural organization of motor control will be described in the following sections. Three levels of neural processing will be explained in the related brain structures of motor system involved in motor control, followed by a description on the neural pathways through which the three levels of motor control communicate. Movement arises from the interplay between three systems including, the sensory/perceptual system, the motor system, and the cognitive system. There are many levels of processing within brain structures that give rise to these systems. The emphasis here will be on the motor system.

Brain structures involved in motor control

The brain structures involved in the motor control are organized both hierarchically and in parallel. The lowest level of the hierarchy of the motor system includes spinal cord, muscles, and sensory receptors. The spinal cord circuitry is involved in receiving and processing the somatosensory information from the muscles, joints and skin. In addition, the spinal cord is the last level of processing before muscle activation. The reflexive movements and also some basic patterns of muscles flexion and extension of the legs movements such as kicking and locomotion are controlled at this level of hierarchy (Ghez & Krakauer, 1991).

The next level of the neural processing is the brainstem, which contains nuclei such as vestibular nuclei, reticular nuclei, and red nucleus. These nuclei play important roles in controlling more complex movements, particularly locomotion and postural control. This part of the motor system receives sensory information from the visual and vestibular systems and somatosensory information from the skin and muscles of the head. The brainstem contributes in controlling movements of the neck, face and the eyes and also is critical in the respiratory movements, arousal and awareness (Ghez & Krakauer, 1991).

One of the brain structures that participates in motor control is the cerebellum. The cerebellum receives inputs from the spinal cord and cerebral cortex and sends outputs to those parts as well as the brainstem. The cerebellum is involved in many important functions in motor control including motor coordination, motor learning and motor programming (Leonard, 1998). The thalamus, as a part of diencephalon, also plays a role in motor control. Information from the spinal cord, brainstem, basal ganglia, and cerebellum must first pass through thalamus. The other brain structure important for motor control is the basal ganglia, set of nuclei beneath the frontal cortex, which are reciprocally connected with the neocortex and with the brainstem. After receiving and processing inputs from cerebral cortex, these nuclei send their outputs back to the cortex via thalamus. The basal ganglia nuclei are generally considered to be involved in planning of motor strategies (Ghez & Krakauer, 1991).

The highest level of motor control is provided by the cerebral cortex. Simple to complex voluntary movements are controlled at this level. Some areas of the cerebral cortex such as the somatosensory cortex, visual cortex and motor cortex, along with other parts of the nervous system are involved in the identification of targets, planning the proper ways of actions and execution of the movements, including movements of the hand in reaching for objects (Ghez & Krakauer, 1991).

The circuitry of the motor system is complex, as is summarized in Figure 1.1. The motor cortex is located in the frontal lobe and consists of three main parts, including the primary motor cortex (Brodmann’s area 4) which is located in precentral gyrus, the premotor cortex (Brodmann’s area 6) which lies rostral to the primary motor cortex (M1), and the supplementary motor area (Brodmann’s area 6) which is located medial to the dorsal premotor cortex and sends projections to the M1 as well as the spinal cord. These motor regions interact with sensory areas, basal ganglia, cerebellum, thalamus, brainstem and spinal cord for the initiation and execution of coordinated movements. The movement of reaching for a target thus does not simply involve primary motor cortex, but

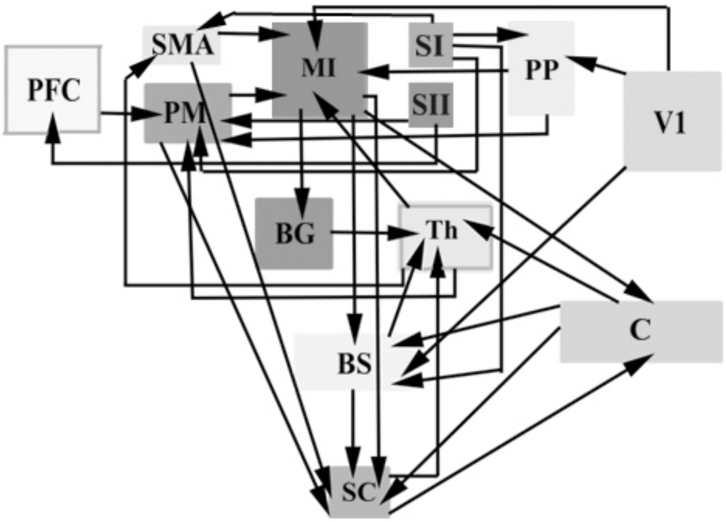

Figure 1.1. Schematic diagram of main connections of the motor control systems. The cortical motor areas are divided into three main regions including, primary motor cortex (M1), supplementary motor cortex (SMA), and premotor cortex (PM). The majority of the cortical projections to the spinal cord (SC) and brain stem (BS) arise in the primary motor cortex. Subcortical regions such as basal ganglia (BG) and cerebellum (C) send projections to the M1 via thalamus (Th). The premotor cortex receives cortical projections from the somatosensory areas (SI, SII), posterior parietal cortex (PP), and prefrontal cortex (PFC).

involves the entire circuit of the motor system (Georgopoulos, 1988; Krakauer & Ghez, 1991).

Although motor cortex is generally considered to execute movement, both premotor cortex and supplementary motor cortex are responsible for motor planning and coordination of motor sequelae. Experimental evidence indicates that the premotor cortex is more directly involved in visually guided sequential movements and the supplementary motor area is more involved in internally generated sequential movements (Halsband, Matsuzaka, & Tanji, 1994). Ventral and dorsal regions of the premotor cortex receive information from posterior parietal cortex and project to the M1 and spinal cord. The primary motor cortex sends motor commands to the basal ganglia and cerebellum for their regulatory feedback and then sends the final motor commands to the brainstem and spinal cord for the execution of movements (Figure 1.2). With respect to an act like skilled reaching, more dorsally located structures are proposed to be involved in the reach to the target and more ventrally located structures are proposed to be more involved in withdrawing the target to the mouth.

The primary motor cortex is the location of large pyramidal cells, called Betz cells, which monosynaptically connected with the motor neurons in the spinal cord. There is a pronounced tradition in research on primates, including humans, that these cells are specifically involved in skilled movements. The levels of activation and involvement of these cells could change depending on several factors including, (1) the types of movement [single joint or multiple joints], (2) speed, (3) the degree of precision, (4) in memorized movements, (5) the initial position of the limb, (6) the requirements of spatial transformation [e.g. moving around obstacles], and (7) the individual’s intent and

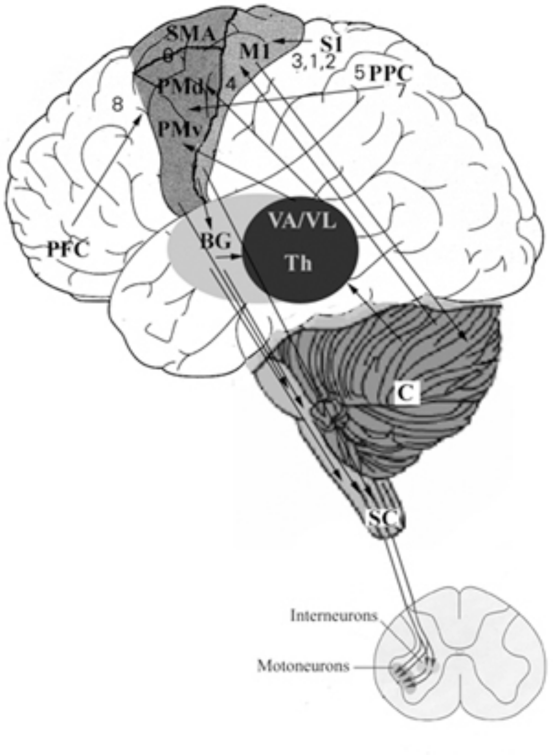

Figure 1.2. Diagram illustrating the motor control areas of the human brain. The primary motor cortex (M1), the supplementary motor cortex (SMA), and the dorsal and ventral regions of the premotor cortex (PMd, PMv) are the main cortical regions of the motor control, which are connected to subcortical areas such as basal ganglia (BG) and cerebellum (C) via the thalamic nuclei (VA, VL). The cortical motor areas can influence the spinal cord either directly or indirectly through the brain stem (Adapted from Gharbawie, 2006 & Ghez & Krakauer, 1991).

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motivation. The evidence supporting these views is that the electrical activity of these cells changes with the changes in the force, the direction of the force, and the frequency of the movement (Georgopoulos, 1994; Georgopoulos, Schwartz, & Kettner, 1986).

Neural pathways involved in motor control

The various motor centers of the brain and spinal cord communicate through several pathways, including corticospinal tract (pyramidal tract), vestibulospinal tract, reticulospinal tract, tectospinal tract, and rubrospinal tract. The corticospinal tract is the main connection between cerebral cortex and the spinal cord and is generally proposed to be the main pathway for motor action. Although the somatosensory cortex projections contribute to the corticospinal tract the main descending fibers arise from the various regions of the motor cortex. The first major connections arise from the M1 and the second one originates from the premotor and the supplementary motor cortex (Dum & Strick, 1991). The fibers descend ipsilaterally through the internal capsule, the midbrain, and the medulla. Near the junction of the medulla and the spinal cord, most of the fibers cross to the contralateral side and form the lateral corticospinal tract and the uncrossed fibers form the anterior corticospinal tract. These projections enter the ventral horn of the spinal cord and make excitatory monosynaptic connections onto α-motor neurons and interneurons. They also make polysynaptic connections to γ-motor neurons and some interneurons. These crossed connections provide the anatomical basis from which each cerebral hemisphere comes to control movements of the opposite hand (Ghez & Krakauer, 1991).

The vestibulospinal pathway originates from the vestibular nuclei of the medulla in the brainstem and project to the spinal cord. The vestibulospinal tract is involved in activating antigravity muscles in the neck, trunk and limbs in controlling of posture and balance. The reticulospinal pathway connects reticular formation in the brainstem to the spinal cord and is important for the autonomic functions and coordination of the automatic movements in locomotion and posture. Also it facilitates or inhibits voluntary movements by affecting muscle tone. The tectospinal tract connects tectum in the midbrain to the contralateral portion of the spinal cord. It mediates reflex postural movements of the head and the eyes. The rubrospinal tract originates from the magnocellular neurons of the red nucleus, crosses to the other side of the midbrain and terminates in the lateral part of the spinal cord. This tract mediates voluntary movements and contributes to the large and fine motor control. The traditional view of its function in relation to the corticospinal tract is that it controls upper arm movements where as the corticospinal tract controls hand and finger movements (Ghez & Krakauer, 1991).

In addition to these main pathways, there are multiple closed loops that contribute to the motor control. The input zone of the basal ganglia, which is the striatum receives inputs from the motor cortex and projects directly and indirectly to the neocortex and provides regulatory feedback. It provides excitatory feedback through its direct pathway, which involves the internal pallidum via the anterior thalamic nuclei and the inhibitory feedback through the indirect pathway involving the subthalamic nucleus and internal pallidum. Another closed loop is formed between the motor cortex and the cerebellum via the lateral thalamic nuclei. However, the projections to and from the cerebellum are not direct pathways and they travel through different regions in the forebrain before the final destination (Ghez & Krakauer, 1991).

Functional organization of reaching movement

Although the description of motor system including the classical neocortical movement regions and their projections to the spinal cord are recognized in all anatomical texts, there are differences in options concerning their functions. In the following section, the functional organization of reaching movement will be discussed.

Three fundamental elements contribute to a successful reaching movement, including selection of a goal, computation of a motor plan of action and production of coordinated forces to execute the reaching movement. These three elements are controlled by cognitive, sensory and motor systems. In addition, the functions of musculoskeletal system also contribute to the control of reaching and grasping movements, which will be described here as well.

A successful reach requires the accurate use of forces (dynamics) and also changes of joint angles (kinematics) relative to the target location, size, and shape. Sensory information helps individuals to locate their bodies (e.g. location of joints relative to each other) relative to other objects including target in the space. In goal-directed reaching, the visual inputs go through two parallel pathways. The first pathway or the ventral stream is related to the perception and recognition of the target and it originates from primary visual cortex and projects to the temporal cortex (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). The ventral stream provides the conscious visual perceptual experience. Visual information plays a significant role in guiding the act of reaching in primates but not in rodents. Instead, olfaction provides critical information for guidance of skilled reaching in rats. Rats are able to determine the location of the food and reach for it accurately in complete darkness and even when their eyes are patched. When the olfaction is blocked rats reaching movements are disturbed (Whishaw & Tomie, 1989).

The second pathway or the dorsal stream is related to the localization of the object (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982). The neural circuitry involved in visuomotor transformation in primates originates from the primary visual cortex where the visual information is encoded and terminates in the primary motor cortex that sends the motor commands for the execution of the movements. During the transformation, visual information is sent to the association areas of the parietal cortex, the anterior intraparietal sulcus and the medial intraparietal sulcus. These regions are known as the parietal reach areas. According to Goodale and Milner (1992) the dorsal stream projections from the visual cortex to the parietal lobe provides action relevant information such as object position, structure and orientation. Evidence has shown that most neurons in the dorsal stream area are multimodal and show both movement-related and sensory-related activities (Andersen, 1987; Schendel & Robertson, 2004).

It is thought that the information related to actions such as various digit and limb postures in reaching is encoded by sending the information to the ventral premotor cortex. The information related to the actions transform into required muscle synergies for the execution of a reaching movement when they are projected to the primary motor cortex (Rizzolatti et al., 1988). The plan is also sent to the basal ganglia and cerebellum for modification and refinement of the reaching movement. The refined and updated motor output plan from the cerebellum is also sent to the M1 and to the brainstem. The motor command descends through corticospinal pathway from the M1 and rubrospinal pathway from the brainstem and terminates in the ventral horn of the spinal cord and synapse with motor neurons and interneurons that control the arm and hands. With the activation of the spinal motor neurons, muscles and joints are synergistically activated to execute the reaching movement. The sensory consequences of the reaching movement are evaluated and updated by the cerebellum when needed. Thus sensory information not only is necessary for making the motor plan but also is important for adjusting the movements and correcting the errors for execution of an accurate reach.

Patients with lesions in dorsal stream pathways show multiple difficulties in reaching movement including problems with reaching in right direction, hand posture and finger positioning. They have problems with adjusting the orientation of the hand and also difficulty in grasp adjustment relative to the object size, shape and orientation, however, they can use the same sensory information to identify and describe the object. On the other hand, patients with the ventral stream lesions has no conscious perception of the size, shape and orientation of the objects and able to pick them up with great adeptness (Goodale & Milner, 1992; Goodale, Milner, Jakobson, & Carey, 1991).

According to Paillard (1982) three aspects of visual information are used in reaching movements, (1) the visual localization of the target in space, (2) the relative position of hand and target, and (3) the motion of the limb across the visual field. Two visual systems are responsible to process and utilize the information related to arm movements. The first system utilizes the central vision to analyze positional information and the second system uses the peripheral vision and analyzes the motion cues, especially self-produced movements (Held & Hein, 1963; Jeannerod & Biguer, 1982; Paillard, 1982).

Mountcastle and colleagues (1975) reported the activation of some cells in the posterior parietal cortex of monkeys occurs during reaching towards extra-personal space and they have called these cells “reaching neurons”. Also Georgopoulos (1986; 1996) has found that neurons in the motor cortex are tuned toward specific directions, and different populations code the direction of the limb movement via excitatory and inhibitory effects. He demonstrated that with stimulation of those neurons, which are broadly tuned toward a specific direction could move a hand that is initially positioned in a location central to the body toward peripheral locations. Initial position and posture of the arm and joint angles as well as speed, force, and muscle activity are the variables that could contribute to directional tuning of the cells (Graziano, 2006; Holdefer & Miller, 2002; Kakei, Hoffman, & Strick, 1999).

Graziano (2006) has proposed that similar directional tuning of cells in the motor cortex are related to ethologically relevant motor patterns. According to his findings, the motor cortex is divided into several subregions. The neurons located within each subregions code for a different category of movement such as central space/ manipulations, reaching movements, defensive movements, hand to mouth movements, climbing and leaping movements, and other outward movements of the arm. He suggested that the topographical organization of the movement could be modified by relevant experience.

Rizzolatti and his colleagues (1996) find that mirror neurons in the motor cortex are associated with goal-directed hand movements, ingestive and communicative movements of the mouth (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). They show that these neurons are not only active during the execution of the movement, for example grasping and eating, but also they are active in recognizing others actions during performance (Iacoboni & Mazziotta, 2007). Two classes of mirror neurons are identified; the mirror neurons, which fire upon the observation of the execution of an exact action and the mirror neurons, and those which fire upon the observation of the similar actions with the same goal (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti & Craighero, 2004).

Visual feedback in reaching adjustment plays an important role in accurate reaching. Studies have shown that the reaches with visual feedback are longer in duration than those performed without feedback. However, the grasp component of the reach movement does not change in the absence of the visual feedback (Jeannerod, 1990). In addition, Fitts and Crannell (1950) found that three factors influence the accuracy of blind reaching, the starting point of the reaching movement, its amplitude, and the movement end point.

As an aside, it is worth noting that reaching can be accomplished without visual cortex. Visual cortical damage to monkeys rendered them blind, but they were able to reach for the objects in or moving across their visual field. It has been shown that the superior colliculus contributes significantly in reaching behaviors in the absence of visual feedback (Humphrey & Weiskrantz, 1969).

Somatosensory feedback also affects aiming movements. The performance of complex movements requiring coordination of many joints for repeating movements with the eyes closed quickly deteriorated in the absence of somatosensory feedback (Rothwell et al., 1982). However, there are various hand movements that can be carried out without somatosensory feedback, such as tapping movements or drawing figures in the air. Therefore, visual and somatosensory feedbacks are essential for programming of accurate goal-directed reaching movements and are responsible for the correct initial direction of the limb toward the target and initial coordination between limb segments.

In addition to neural control, musculoskeletal systems also contribute significantly to the reaching and grasping movements. Musculoskeletal systems include muscle properties such as muscle tone and strength, joint range of motion, and biomechanical relationships between linked body segments. Different types of joint motion are required for the ability to reach and grasp, including scapular rotation, appropriate movement of humeral head, ability to supinate the forearm, flexion (100-120 degrees) of the shoulder and elbow, ability to extend the wrist and sufficient mobility of the hand in performing grasp and release (Charness, 1994). In humans the upper arm that generates a wide range of movements is connected to the shoulder by a joint. The same range of movements can be seen in rats with scapula tethered by muscles. Limb musculature is similar between rats and humans. Although rats have intrinsic muscles in their hands, their movements are controlled and supplied by forearm muscles (Whishaw, 2005).

The hand in both humans and rats is specialized to play a significant role in reaching and grasping. They not only use hands in feeding movements but also in manipulating objects and communication. Grasp patterns vary based on the size, shape and location of the object to be grasped (Johansson & Edin, 1992). Napier (1956) classified grasping movements in two classes, power grasp and precision grasp. He believed that not only the object shape and size would affect the grip pattern but also the intended activity would determine the grasp pattern as well (Jeannerod, 1996; Napier, 1956). The pincer grasp, which is thought to be exclusive to the primates, involves the thumb moving in opposition to one of the other fingers, usually the index finger, and it allows fine manipulation of tiny objects. The rat does not display a pincer grasp when reaching and so its reaching and grasping movements are equivalent to the primate power grasp.

Individual differences

The study of individual differences in motor skills has been neglected in investigations that use rats as their models. Individual variation in motor performance is usually classified as an error variance and experimenters predominantly only consider the group data. Obviously individual differences are important factors in experimental paradigms and failure to consider individual variation discards valuable information and reduces explanatory power. The following sections will describe: the neurobiology of individual differences characteristics, the factors related to individual differences in motor performance, and individual differences in motor abilities and skill acquisition.

Neurobiology of individual differences

People differ in terms of aptitude, attitude, motivation, and temperament and these variations are caused by differences in the physical and chemical structure of the brain. Brain differences are the neurobiological base for the individual differences found in perceptual, cognitive and motor responses. The sources of brain variations are both genetic and epigenetic. The genetic makeup of an individual has its origins in the half of the genome received from the mother and the half of the genome received form the father (Dunn & Plomin, 1990; Schumann, 2004).

According to Edelman (1987) a developing nervous system is not simply specified by genes. Genes respond to the local chemical environment to control the expression of adhesion molecules that influence the differentiation, migration and connections of neurons. Thus, three sources of individual differences might be recognized: 1) developmental selection may lead to roughly similar brain construction but with potentially different microstructure, 2) the establishment of "primary repertoire" or the basic neuronal groups and their connections by the activity of adhesion molecules, 3) experiential selection, resulting from an individual's postnatal interactions with his/her environment. During this stage, there are vast changes in the brain including shedding of synaptic connections, pruning of dendritic trees, and even the substantial loss of neurons. Experiential selection generates more differences between individuals because of the difference between individuals' environmental experiences. In addition, the interaction between the environment and intrinsic growth mechanisms generates more variation in neuronal structure (Edelman, 1987, 1992; Quartz & Sejnowski, 1997; Schumann, 2004).

According to Darwinian view, the differences in brains are selected by environment and facilitated by experience within the environment. For example, the best athletes are those individuals with particular neuro-hypertrophy who developed their motor skill in a proper environment. If these particular neural strengths are not selected and used in an environment, then they would not be recognized as super talented athletes. Evolution permits environmental selection on the inter-individual variations of the nervous systems. The diversity and adaptability of the nervous systems to the constantly changing environment are the results of natural selection and both increase the chance of survival (Schumann, 2004).

Factors related to individual differences in motor performance

Motor skill is defined as specific physical movements required for accomplishing the goal of a particular task. Motor skills vary from simple to complex and are most often composed of series of distinct movements that need to be learned and performed in specific orders. The term of motor skill has been used in literature in two different ways: 1) it is used as an act or task, such as piano playing, swimming or reaching toward an object, 2) it is also used as an indicator of quality of performance, which is determined by the degree of proficiency or productivity of the performance. A performer can be called "skillful" or "skilled" when his performance meets several criteria. First, his performance should lead to successful outcomes. Second, during learning the performer uses the relevant and meaningful cues in guiding the movements skillfully and is not distracted by other cues that are not important for skill acquisition. Third, the performer should be able to anticipate the subsequent movements for better responding (Magill, 1985).

Motor skill should be distinguished from motor ability. According to Schmidt (1975) motor abilities are " hypothetical constructs thought to be innate and relatively stable characteristics of the individual that underlie a certain type of motor response". Skill is more specific and easily modifiable by practice. The earliest idea about motor abilities was the idea that all motor skills, ranging from simple to complex, are developed on the basis of a single motor capacity known as, general motor ability (GMA). This view is similar to Pearson’s idea about the nature of intelligence, which was a general intellectual capacity. Individuals with “high” GMA are able to perform well on almost every motor task and individuals with “low” GMA were destined to fail in almost every motor task. This hypothesis predicts that individuals with better performance in one motor skill should be the good performer on other motor skills (Sheridan, 1985).

Opposition to the GMA notion came from correlational studies. During 1950s and 1960s many studies showed very low correlations between motor tasks, even motor tasks that have a strong resemblance (Schmidt, 1975). The specificity hypothesis presented by Henry (1968) also opposes the GMA hypothesis. Henry hypothesized that there are a large number of motor abilities responsible for motor behavior, each of which are involved in limited number of movements. These motor abilities are independent of each other. Based on this hypothesis, success in a performance depends on the “quality” of abilities involved in that movement. Therefore, because of the independence of abilities, high quality performance in one motor task does not guarantee the quality of the performance in another task (Henry, 1968).

Fleishman’s (1965) ideas on motor abilities positioned him between these two extreme thoughts. Using factor analysis statistical techniques, he outlined some abilities as clusters of skills that are correlated with each other such as control precision, multi-limb coordination, etc. that underlies motor performance. He believed that these abilities are not task specific but they are a prerequisite for successful performance.

Motor performance in the earlier theories was not distinguished from motor learning. It was usually thought that the changes in motor performance during practice were due to motor learning per se (Schmidt, 1992). Motor performance can be defined as a temporary change in the observed motor behavior during practice sessions (Shumway-Cook & Woollacott, 2001). However, performance is an interaction between variables such as learning, motivation, anxiety, fatigue, and many others.

Individual differences in motor abilities and skill acquisition

The nature of individual differences in motor abilities and skill learning was questioned early in the history of modern psychology. Early investigators tried to answer the fundamental question about the effects of nature versus nurture on motor behavior and skill acquisition. In explaining the differences in motor performance and appearance of various phylogenic skills, the investigation of individual differences in skilled movements has traditionally been dominated by the issue of capacity based on maturation rather than experience and interaction with the environment. Although initially maturation may seem to be a significant contributor to the onset of phylogenic skills it is very difficult to rule out experiential factors on the development of even fundamental actions.

Thorndike (1908) was perhaps the first investigator to try and examine the similarities and differences between individual performances after extensive practice. He thought if nature or genes are the primary determinants of the individual's performance, after extensive practice individuals should reach their optimum and reveal the genetic contribution variation in task performance. On the other hand, he proposed that if nurture or experience were the primary determinant of the performance, the result would be a reduced variability in performance (Boyle & Ackerman, 2004). The major concern of the investigators in this field is the problem related to the assumption that underlying abilities required for tasks are the same (Ackerman, 1987; Adams, 1987).

Individuals encountering a new task usually transfer some prior knowledge and relevant abilities (Ferguson, 1956). According to Schmidt's schema theory, the transfer to a novel task can be increased with more variability of practice (Schmidt, 1975). The degrees of prior knowledge and the task relevant abilities are different among individuals. Because of the differential transfer, the amount of time for familiarization with the new task and also the degrees of learnt skill would be different. There is a common finding for many skill acquisition tasks that in terms of the difference between initial and practiced task performance, the subjects with poorest performance tend to improve the most with more practice. Such negative correlation between initial performance and performance improvement after practice is explained partly by the fact that better performers at the beginning of the training are those with better repertoire of abilities that they can positively be transferred to a new task. In other words, the good performers with better start in a new task will travel a shorter distance on a learning curve than the poor performers.

The final performance levels also are related to the initial transfer as well as the amount of learning of the new skill. In addition, non-ability characteristics (motivational and affective traits such as self-efficacy, high/low level of anxiety or motivation) play important role in individual differences in skill acquisition. For example, high level of anxiety might be detrimental to learning because it leads to distraction of attention, which is required for better learning during initial phase of acquisition (Kanfer & Heggestad, 1999).

According to Henry (1958) individual differences in the ability to learn one motor skill are not predictive of ability to learn other motor skills. He suggests that although there are some common factors in motor skills that could facilitate the learning, the transfer process is not a skill-to-skill transfer. Fleishman (1965) also points out the importance of the ability-to-skill transfer in his theory. He proposes that an individual's ability to learn a motor skill is largely determined by the individual's possession of the perceptual-motor abilities required for that particular skill. Thus, those individuals with more highly developed perceptual-motor abilities can become proficient in several relevant motor skills. He assumes that skill specificity limits the amount of transfer that can be expected between different motor skills.

Cratty (1966) in his "Three-level Theory" attempted to organize factors that contribute to individual differences. His theory is conceptualized as a triangle with base, midsection, and apex for the three levels of factors influencing the performance. The base level consists of the individual's traits, which influence all kinds of behavior and the individual's level of arousal and general aspiration level. The second level is the location of perceptual-motor abilities such as strength, flexibility, and speed required for performing motor skills. The last level, on the apex of the triangle, is the level of factors (neuromuscular/environmental) specific to a particular skill such as unique spatial-temporal pattern of movement or unique situation under which the skill is being performed.

Adams (1987) proposes that different abilities become important in relation to the early or late (experienced) performance on a skill task. Early performance is determined by general cognitive ability while later performance is determined by the task-specific ability. The only way of predicting the skilled performance on a task is the measures taken from that particular task, not other tasks or abilities prior to training (Fleishman & Hempel, 1955). They believe that the best performers cannot be identified from measures for general abilities on the early stage of skill acquisition prior to practice. However, there are other others who disagree with this notion (Ackerman, 1989; Barrett, Alexander, & Doverspike, 1992; Hulin, Henry, & Noon, 1990). For example, Ackerman (1987) finds that individual differences in skilled performance after extensive practice are related to the perceptual, cognitive and motor abilities and could be predicted even prior to the extensive practice with proper measures and statistical procedures.

According to information-processing theory, performing a new task is effortful and needs longer time for processing but after practice and learning the task, it changes into more automatic processing (Ackerman & Schneider, 1985; Schneider & Shiffrin, 1977). Thus, a task requires continues attention and control over performance at the beginning of training because of the novelty of the task. With extended practice, the task can be performed with the minimum amount of attention due to acquired automaticity. The transition from learning new components of the task to the formation of strong associations between information and responses forms the framework of skill acquisition. Thus, skill emerges out of the consistent attributes of the task and extensive practice (Fitts & Posner, 1967).

Individual differences can be measured by specific tasks for a wide variety of abilities and traits. Three major measures are usually the focus of the studies of skill acquisition: (1) initial performance, (2) rate of skill acquisition, and (3) asymptotic skill level (Boyle & Ackerman, 2004). According to the three-phase theory of individual differences in skill learning proposed by Ackerman (1988), skilled performance of more consistent tasks becomes more automatic after practice. During the first phase, attention and cognition are very demanding and performance is slow and is associated with many errors. At this stage, an individual encountering a novel situation uses its reasoning skills and general intelligence to evaluate the situation and learn the rules and basics related to the task. Thus, at the first phase of the skill acquisition, general intelligence is the main determinant of individual differences in performance. The second phase is important for integration and consolidation of the collected information. During this phase of learning, perceptual speed abilities are the most important determinants of the individual differences in performance. Thus, the individual encodes consistent patterns rapidly and compare them for better response and forms stronger associations between information and responses. The third phase of the skill acquisition occurs during the late stages of practice. At this stage, the performance is mostly motor response and free of perceptual processing of information. Skilled performance gets automatic and effortlessly executed while approaching the asymptotic level.

This theory suggests that general ability used in phase 1 is highly correlated with the early performance and declines with practice. However, perceptual speed abilities used in phase 2 are not correlated with performance initially but increases with the formation of stronger associations and decreases again. In phase 3 psychomotor abilities comes into play and are correlated with the late performance, which is characterized by on rapid responses.

Clearly, the research on motor skills suggests that it is difficult to parse performance into components that are attributable to individual differences in any one factor, even though individual differences in performance emerge. Perhaps developing simpler models could be beneficial for understanding individual differences. Thus, this thesis has attempted to develop a simple animal model of motor performance. The skilled reaching behavior of the rat, which is the animal model to be used here, will be described in the following section.

Skilled reaching

The hand in humans and rats are specialized body parts, and of course, play significant role in reaching and grasping. Hands are used not only for manipulating objects that can facilitate feeding process but also are useful in our communication. According to Napier and Tuttle (1993) each finger (except the thumb) composed of three phalanges that are able to flex by the joint which connect them together. Small and precise movements of fingers occur with the movements of tendons that are attached to the forearm muscles. Flexion and extension of fingers provide numbers of hand postures such as poke, pinch, clench, and palm and make the object manipulation possible. The differentiation of the hand postures happens in the pre-shaping of the grasp phase during the transportation component of the reaching (Jeannerod, 1996; Klatzky et al., 1987). Therefore, two important factors are required to make a successful grasp. Appropriate hand posture based on the shape, size and the use of object, and appropriate timing of the finger closing on the object during reaching movement (Jeannerod, 1990).

Skilled reaching is a behavior in which an animal reaches for a piece of food and places it in the mouth for eating. The behavior is also sometimes called reach-to-eat. Skilled reaching for food by rats has been studied extensively in order to obtain a better understanding of neural and functional organization of the movement. The behavior has also been used to assess the behavior after brain injury and to evaluate effects of therapeutic interventions. Although skilled reaching is widely used to model a variety of neurological conditions, there has been little attention directed at individual differences in reaching performance of the rats. This section of the thesis will describe the evolution of skilled reaching; skilled reaching in the rat; and neural plasticity associated with skilled reaching following different conditions such as motor cortex injury.

The evolution of skilled reaching

Many psychologists, including William James, have noted that all behavior, including psychological processes, can only be recognized through movement. Because this thesis is directly concerned with individual differences in reaching behavior, it will be helpful to have a definition of the reaching movement.

As note above, skilled reaching is an act in which a hand is used to grasp food and place it in the mouth for eating. As such, it is a complex action that requires the cooperation of several brain systems including motor systems, sensory systems and cognitive systems. The motor system plans and executes the reaching movements. Sensory systems provide information about the location of the body in space and the location of objects in the environment. Cognition integrates perceptual events and movement to provide a holistic and individual perspective. The sensory and cognitive information is integral to the motor ability and is necessary in production of an effective and successful movement in an environment (Rosenbaum, 1991).

A wide variety of animal species display skilled reaching. A phylogenetic analysis of animals that display the behavior suggests that it likely evolved in the earliest terrestrial vertebrates (Iwaniuk & Whishaw, 2000). Nevertheless, forelimb dexterity have been lost in some mammalian species such as polar bears of the family Ursidae and have been more developed in some other mammalian orders such as primates (Iwaniuk, 2000). The rodents and primates appear to be the groups that are most adept for using the forelimbs to reach (Whishaw, 2005).

The origins of skilled reaching movement are not well understood, but it may have evolved in part from a number of different precursor behaviors. Skilled reaching may have developed by the modification of movements required for locomotion. Thus, reaching for an object may simply be a modification of the movement of the forelimb to grasp the ground while walking. It may also have evolved as a modification of movements used for feeding. For example, an eating animal may make movements of “wiping” [movements of the palms, which are used to push the prey towards the midline], “scooping” [the movements with the extension of the digits and use the back of the hand to push the food into the mouth], and grasping [movements of the closure of digits on the prey to bring it toward the mouth] (Iwaniuk & Whishaw, 2000). Reaching may have also evolved as a modification of stepping movements in arboreal animals that use the forelimbs to grasp branches. These and other influences are not mutually exclusive, and each may have shaped the specialized behavior of different species.

It is clear that skilled reaching has been modified substantially in its evolution and the evolutionary history of the movement may be partly different in different orders of animals. Nonprimate species of animals do not appear to use vision to direct their limbs toward objects, whereas primates do use vision. To locate food prior reaching and preshaping digits for grasping (Figure 1.3), rats use olfactory and tactile information (Whishaw & Tomie, 1989; Whishaw, Dringenberg, & Pellis, 1992). In testing conditions in which visual inputs are blocked, rats can quickly and successfully locate the food as they do in normal situations but with the elimination of olfaction the reaching movements of the rats are disturbed. However, the guidance of the forearm toward the food is not controlled by olfaction but rather by central control (Whishaw, 2005). Metz and Whishaw (2000) suggested that the skilled reaching displayed by rats is organized as an action pattern because of similarity, consistency and being recognizable from instant to instant and also because of its disruption after the task demands are altered.

Bloch and Boyer (2002) suggest that specialized grasping evolved before the capacity to control reaching visually. They suggest that animals were first able to make anchors for stability using their hindlimbs and forelimbs. Thereafter they began to use the forelimb to grasp objects. They further suggest that this kind of feeding contributed to the forward binocular configuration of the eyes of primates. Therefore, the accurate control of reaching with vision may have occurred early in primate evolution. All primates do use vision to guide a hand to a target object.

The difference between rodents and primates is important with respect to the objects of the present thesis. In order to reach for an object, a rodent must compose and execute a motor plan. As will be described in the thesis, rats are not always successful in obtaining food, and their inaccuracy provides a measure of skill and therefore insights into individual differences. Because reaching is guided online in primates, they are often successful and there is low variance in the performance of the animals that would allow for the study of individual differences.

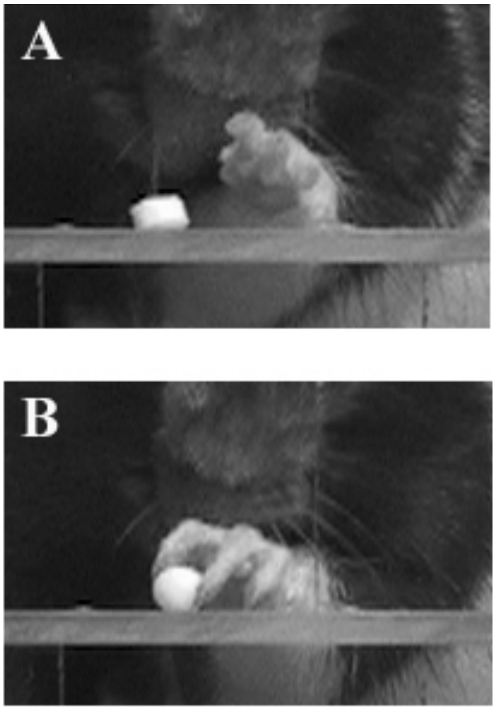


Figure 1.3. Reaching and pre-shaping of the digits during grasp movement in rats. (A) the digits are extended during advance part of the reaching movement, and (B) the digits are pre-shaped for the grasping movement during arpeggio when the hand pronates from digit 5 (the outer digit) through to digit 2, while simultaneously the digits are opened.

Skilled reaching in the rat

Peterson (1934) was amongst the first scientists to describe reaching behavior in the rat using a task in which the animals reached to take food from a tray. The animal is now widely used to study skilled reaching. This section will first describe the anatomical basis of skilled reaching in the rat, then describe tasks used to study skilled reaching, and conclude with exemplar research in which rat skilled reaching has been used to study neural plasticity.

The anatomical basis of skilled reaching

Limb musculature is similar between rats and humans. Although rats have intrinsic muscles in their hands, their movements are controlled and supplied by the forearm muscles (Whishaw, 2005). The number of digits and phalangeal composition in rat's hand is similar to that of human. A rat's hand has five digits, a small thumb with nail (digit 1) and four other digits with claws (digits 2-5). The capability of medially movements of the thumb (digit 1) toward the palm and the extent of flexion and extension of the digits show that they are able to manipulating fine objects such as a strand of uncooked spaghetti. Rats are able to make the pincer grips that are made by opposition between the thumb and digit 2 and also the scissor grasps that are formed by opposition between digits 4 and 5 (Whishaw, 2005; Whishaw & Coles, 1996).

The overall neural organization of motor control in rats is similar to humans. There are three anatomical distinctive neocortical regions in rat's brain, including agranular zone, granular zone, and dysgranular zone, which play significant role in sensory and motor control (Figure 1.4).

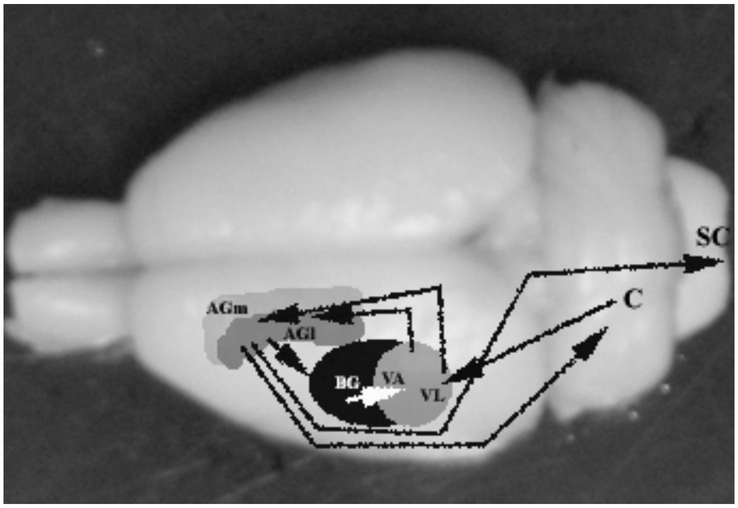


Figure 1.4. Diagram illustrating the motor control areas of the rat brain. The main motor cortical areas of the rat brain are the agranular medial cortex (AGm) and the agranular lateral cortex (AGl). These regions are connected with the subcortical regions such as basal ganglia (BG) and cerebellum (C) via thalamic nuclei (VA,VL). (Adapted from Gharbawie, 2006).

Based on the similar neurophysiological properties, the primary motor cortex of the human is similar to the lateral agranular neocortex (AGl) of the rat frontal lobe (Wise & Donoghue, 1986). This area contains a larger layer of pyramidal cells and is the origin of the corticospinal projections. The AGl similar to the M1 forms closed loops with the basal ganglia and the cerebellum.

The premotor and supplementary motor areas in primates share the similar anatomical and electrophysiological properties with agranular medial neocortex (AGm) in rodents (Neafsey et al., 1986; Sievert & Neafsey, 1986). The sensorimotor cortex is located lateral to the AGl and support sensory and motor functions. This area is a dysgranular zone with a less-dense and thinner layer 4. Lateral to the dysgranular zone is the granular zone, which extends as far as insular cortex and is distinguished by its elaborative layer 4. This area receives sensory inputs from the ventral posterior nucleus of thalamus (Wise & Donoghue, 1986).

The corticospinal fibers in rats take a somewhat different route than those of primates. Most of the fibers exit the cortex and immediately enter the internal capsule and the remainder project through the striatum before entering the internal capsule. Corticospinal fibers descend in the base of the dorsal horn of the rat spinal cord and entering the spinal gray matter and synapse in the intermediate zone. The corticospinal fibers do not make direct connections with the motor neurons of the spinal cord but synapse on pools of interneurons (Lemon & Griffiths, 2005).

Tasks used to study skilled reaching in rats

Numerous reaching tasks have been used for investigating skill acquisition (Greenough, Larson, & Withers, 1985; Kleim, Barbay, & Nudo, 1998; Montoya, Campbell-Hope, Pemberton, & Dunnett, 1991; Whishaw, O'Connor, & Dunnett, 1986; Whishaw & Pellis, 1990), handedness (Peterson, 1934; Peterson & Gucker, 1959), and identifying impairments and recovery of function after lesions to the cortical and subcortical areas (Whishaw & Gorny, 1996; Whishaw, O'Connor, & Dunnett, 1986) especially motor cortex (Gharbawie, Gonzalez, & Whishaw, 2005; Gonzalez & Kolb, 2003; Whishaw, Pellis, Gorny, & Pellis, 1991).

The tray-reaching task as a simple test of forelimb use (Whishaw, O'Connor, & Dunnett, 1986) provides a relatively easy assessment of a rats preferred hand and its reaching ability. Rats are placed in the tray reaching boxes measured 10 cm long, 18 cm wide, and 10 cm high (Figure 1.5). The tops, backs, and sides are made of transparent Plexiglas. The front of the box is constructed of 2 mm bars that are separated by 9 mm distance. Rats reach through bars into a 4 cm wide and 5 mm deep tray, mounted in front of each box and extended for the length of the box, filled with granules of food (chicken feed or small food pellets). The floor of the boxes is made of metal grids, so that dropped chicken food would not be accessible to the rat. Reaching performance is assessed based on the number of success or failure. Similar to the other reaching tests, this test has some advantages and disadvantages. The possibility of simultaneous testing of several rats as well as un-accessibility of the dropped food pellets (because of the wire grid floor) is among advantages of the task. One of the limitations of this test is the lack of power for detailed analysis of the limb movements. Such limitation is mainly due to the structure of the apparatus that provides greater options for the rats to insert their forelimbs from

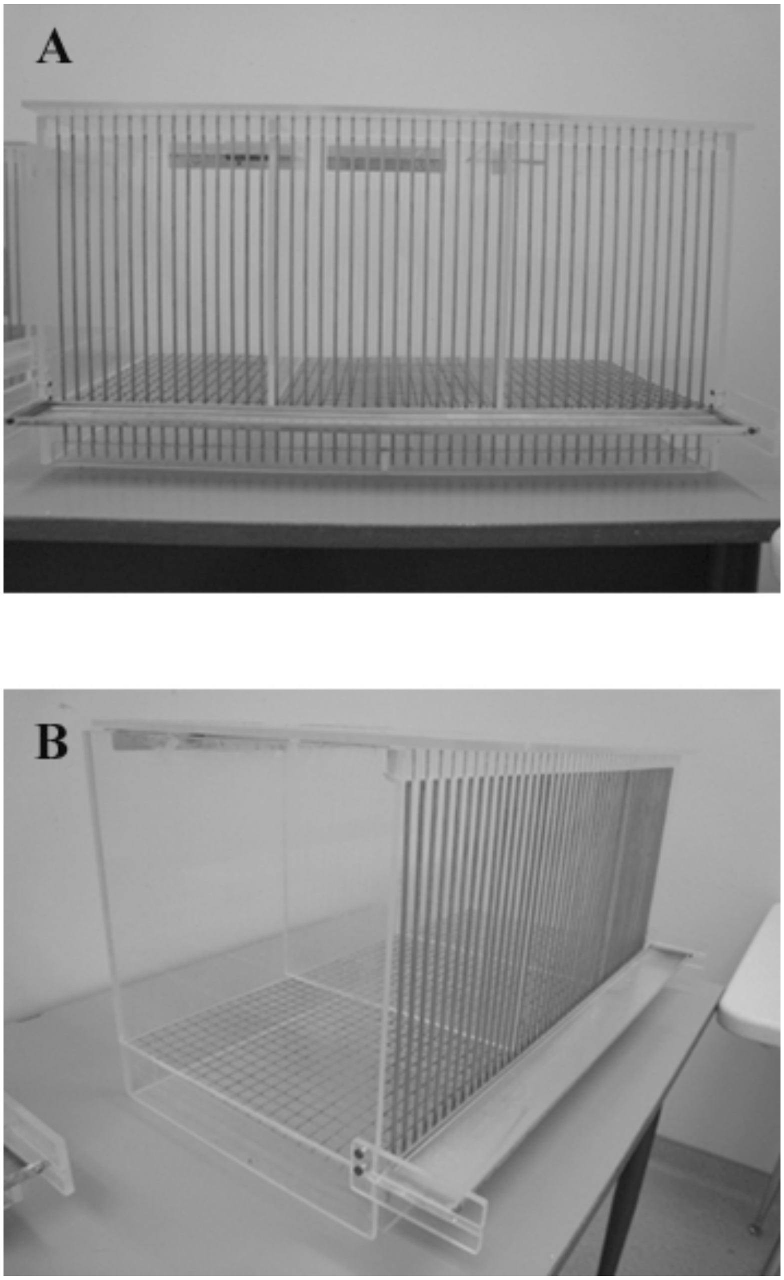


Figure 1.5. Tray-reaching apparatus. (A) front view of three attached tray-reaching boxes, (B) angular perspective of the apparatus for better view of the inside of the box as well as the food tray and metal grids floor.

different angles between the bars and from various possible body postures. This condition does not allow a controlled observation and scoring of the limb movements while reaching.

The staircase test (Montoya, Campbell-Hope, Pemberton, & Dunnett, 1991) is designed to assess both forelimbs in a single testing session. Rats are placed on a platform to reach for food pellets on the steps (7 steps in total) of a staircase on either side. Because only the number of pellets remaining on the stairs is counted as a behavioral measure, several rats can be assessed concurrently. The difficulty of the task is ranged from easy to hard in terms of the possibility of various reaching targets with different distances (closer vs. farther steps). Although this task has some advantages such as time efficiency and high range of reaching assessment such as side bias, maximum forelimb extension, and grasping movements.

The single pellet-reaching task is a reliable measure of reaching performance in which rats reach through a slot for a single food pellet each trial. Every session consists of 20 trials in total. Discrete trials are established by the experimenter via withholding the food pellet at the end of each trial and shaping the rats behavior to leave the slot, walk to the rear wall of the box, turn and approach the slot again for the next pellet, allowing the animal to reposition its body for the next reach.

The single pellet-reaching box (Figure 1.6) is made of transparent Plexiglas with 45 cm length, 14 cm width, and 35 cm height. In the middle of the front wall, a 1 cm wide slit is extended from bottom of the box to a height of 15 cm. A 2 cm wide by 4 cm long shelf is attached to the outside of the front wall, 3 cm above the bottom of the box in front of the opening. There are two small indentations with 1.5 cm distance from the front

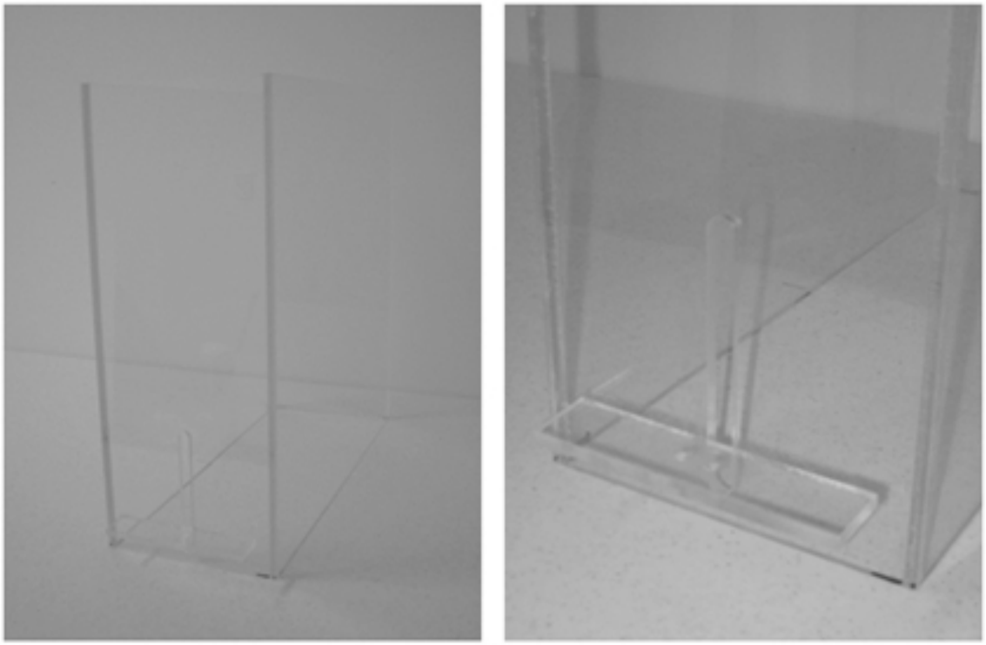


Figure 1.6. Single pellet-reaching apparatus. (A) full view of the single pellet-reaching box, (B) close up view of the shelf and the slot on the front wall of the reaching box.

wall aligned with each side of the slot to hold the food pellets. A food pellet in each indentation is accessible only to the contralateral hand, because it pronates medially to grasp. Reaching performances are assessed quantitatively in terms of the number of attempts, single reach successes, and total success (Whishaw, Pellis, Gorny, & Pellis, 1991).

A successful reach is a reach attempt in which the food pellet is grasped following the advancement of a forelimb through the slot, which is followed by its withdrawal toward the mouth and obtaining the food by the rat. Success in single pellet reaching task requires greater precision and higher motor control relative to other reaching tasks perhaps partly because the range of movements required to successfully perform this task is much more limited than other tasks, which provide a challenging condition for the performers. Therefore, this task makes individual differences more noticeable. The transparency of the reaching box makes video recording possible from different angles and facilitates kinematic analysis of the reaching movement and also analysis of the body posture during the performance.

The skilled reaching is a voluntary goal-directed behavior, which is controlled by perceptual, cognitive and motor systems and become automatic with extensive practice (Dickinson, 1985; Halsband & Freund, 1993). The skilled movements in rats are the movements of forelimbs, hands, and digits for catching, manipulating, and holding objects, which is a well-developed behavior in almost two thousand rodent species (Whishaw, 2005).

Although individual differences in skilled reaching performance of rats have not been studied systematically, there are several studies showing differences in skilled reaching of various strains of rats. Nikkhah and colleagues (1998) described the strain differences in successful reaching in the staircase task. They reported that outbred albino Sprague-Dawley rats were the most successful reachers among others. Although, it has been shown that Sprague-Dawley and Long-Evans rats displayed equivalent reaching success on the single pellet-reaching task, the movements used are different between these strains (Whishaw, Gorny, Foroud, & Kleim, 2003). Also, the study of strain differences in topographical representations of movements between Long-Evans and Fischer-344 suggested that the Long-Evans rats showed a relatively larger cortical representation for movements as well as higher reaching success and more organized movements relative to Fischer-344 strain (VandenBerg, Hogg, Kleim, & Whishaw, 2002).

Behavioral manifestations of individual differences can be measured by some specialized tests. Movements can be analyzed at three levels including (a) action, (b) movements, and (c) neuromotor processes (Gentile, 1992). There are different facets in every movement, which can be analyzed at these three levels. A combination of information gathered by these analyzing methods will provide a better understanding of the considered movement.

According to Gentile, analyzing a movement at the action level examines the behavioral outcome in various categories including, accuracy, speed, and response magnitude. The outcome of a movement is not separable from the form of the movement and a successful outcome can be achieved from a good form of the movement although there is no guarantee. Thus, the second method of analysis is focused on movement elements used in the performance. A movement also can be studied at the neuromotor level. Gentile (1992) suggests that a specific movement could be analyzed based on its underlying neural processes. In a goal-directed action, one can use different strategies in performing an action towards the selected target that are called movement equivalence and also there are many ways to organize underlying systems to achieve a specific motor pattern, which are called motor equivalence (Bernstein, 1967; Gentile, 1992; vanSant, 1988). Therefore, a skilled movement is defined by the ability to adapt movements to successfully and efficiently achieve the goals or avoid the harms in a constantly changing environment. Although these three levels of analysis are very important in assessing a movement, but it needs to be mentioned that the observed movement is determined by the interaction of three factors, including the individual, the task, and the environment (Shumway-Cook & Woollacott, 2001).

For a better understanding of the movement elements in rat's skilled reaching, different methods of analysis have been used. For example Eshkol Wachmann Movement Notation (EWMN) is used to describe the relations of body segments (Whishaw & Pellis, 1990), and Laban Movement Analysis (LMA) for describing qualitative aspects of movement (Whishaw, Gorny, Foroud, & Kleim, 2003). Rats are required to fixate some parts of the limb in order to move other parts. For example, when rats bring their digits to the midline of its body, they are fixed to that location while its elbow moves to the midline position (Whishaw, 2005). Skilled reaching movement is subdivided into 10 movements including, (1) digits to the midline, (2) digits flexed, (3) elbow in, (4) advance, (5) digits extend, (6) arpeggio, (7) grasp, (8) supination I, (9) supination II, and (10) release (Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993). Each of the 10 reaching elements is rated on a three-point scale (0, 0.5, 1) to obtain movement scores. A score for a normal movement is “0”, a score for an abnormal movement is “0.5”, and the score is “1” in the absence of the movement. Also, LMA provides a method for quantifying the non-kinematic features of movement (Foroud & Whishaw, 2006). Reaching consists of a sequence of four gestures including (1) advance, (2) grasp, (3) withdrawal, and (4) release. Each gesture is separated by a brief pause and change in the movement direction and speed (Alaverdashvili, Foroud, Lim, & Whishaw, 2008). Typically in a successful reach, each of these gestures is performed once in a complete reach sequence (advance-grasp-withdrawal-release), but gestures can also be repeated several times in a successful reaching movement. Counting the number of gestures performed in a reaching movement is another variable used for measuring the skilled reaching performance.

Neuroplasticity and skilled reaching

Individual differences in performance must have their origins in some aspect of the morphology of animals. Given the equivalence in general morphology, a likely origin is in neuroplasticity of the brain and skilled reaching in rats has been extensively associated with studies of neuroplasticity. This section will summarize some of the literature on skilled reaching and neuroplasticity, especially with the aim of pointing out that measures of reaching success are generally viewed as relevant to understanding motor learning and neuroplasticity.

Motor learning emerges from a complex of perception, cognition, and motor processes. Animals with the use of motor learning can achieve valuable and beneficial goals and avoid harms. According to Schmidt (1988) motor learning has several characteristics, (1) motor learning is a set of underlying changes that happen only with practice, (2) it produces capability for particular movement, (3) the processes of learning is not a change in behavior per se, but it is the internal capability for responding, (4) motor learning is relatively permanent and is different from a variety of temporary performance factors such as fatigue or high/low levels of motivation. Therefore, according to Schmidt, motor learning is defined as a set of processes associated with practice or experience that leads to relatively permanent changes in the capability for movement.

Schmidt's definition describes only one form of motor learning, which is skill acquisition. Shadmehr and Wise (2005) have an expanded view of motor learning, which includes three forms of motor learning: (1) an evolutionary form of motor learning that passes through generations and contributes directly to biological fitness with allowing animals to associate neutral stimuli to stimuli that trigger instinctive reactions, (2) skill acquisition (gaining a new level of motor performance) and motor adaptation (regaining a given level of motor performance), and (3) learning how to make decisions for selecting goals and the required movements in order to reach that goals.

According to Shadmehr and Wise (2005) motor learning over generations involves many autonomic and neuro-endocrine functions as well as many aspects of procreation, foraging, exploration, defense and ingestion. These instinctive behaviors are learned through mechanisms that are not based on an individual's experience and encoded genetically and reproduced over generations. Some of these behaviors can be modified to various degrees by an individual's experience and some are not flexible at all.

Animals also use a learning mechanism involving the prediction of sensory inputs associated with potential harm or benefit which is triggering some somatic reflexes in response to that prediction. This response range form simple autonomic reflexes to the movement of a whole animal body. The moving behavior of an animal toward a stimulus associated with a reward such as food is called approach behavior and the moving behavior of an animal away from a stimulus associated with harm is called fear conditioning. This learning mechanism underlies fundamental behaviors including feeding, fleeing, fighting, and mating (Shadmehr & Wise, 2005).

In everyday life, animals must behave adaptively in a changing environment by extending their motor repertoire and adapting the new and existing motor programs for a successful living. Two types of motor learning, skill acquisition and motor adaptation, contribute to the movement stability and control. Skill acquisition involves expansion of the motor performance beyond prior limits of the system that is developed by the interaction of systems involved in selecting the target, computing a motor plan, and generating the coordinated movements. On the other hand, motor adaptation can be defined as a modification in motor performance to regain capabilities in changing circumstances (Shadmehr & Wise, 2005). Motor skills are acquired gradually through practice and interactions with environment. Studies have shown that the acquisition of motor skills follows two distinct phases: one an early and fast learning phase in which considerable motor improvement can be measured within a single learning session, the other is a later slow learning phase in which more motor improvements can be observed across training sessions (Karni et al., 1998; Nudo, Wise, SiFuentes, & Milliken, 1996). Different variables are used to measure motor skill learning such as a reduction in reaction time, the number of successes or errors, and/or a change in movement synergy and kinematics (Ungerleider, Doyon, & Karni, 2002). Investigators measure both skill acquisition and motor adaptation to study the neural substrates mediating motor skill learning (Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Karni et al., 1995).

In a changing environment, advanced animals must be capable of adapting behavioral repertoire in that environment. According to Balleine (2001) both prediction and control are required for a successful adaptation. Pavlovian conditioning as a form of predictive learning is used to elicit anticipatory responses to some stimuli based on establishing associations between them (Balleine & Dickinson, 1998; Hammond, 1980). With the use of predictive learning animals are able to control their responses toward gaining access to benefits or avoiding from harms. Therefore, for a successful adaptation, the innate behavioral repertoire must be modified through skill acquisition and actions must be learned and selected based on their potential consequences (Balleine & Dickinson, 1998). The decision-making process as a part of motor learning is essential for movements particularly reaching movements.

Before starting many of our movements such as reaching, goals must be selected consciously among several options. Also there are other movements that are controlled subconsciously and could be seen as simple sensorimotor transforms such as habits (Graybiel, 2008; Shadmehr & Wise, 2005). It is thought that a skilled behavior becomes resistant to both interference and passage of time with extended practice (Ungerleider, Doyon, & Karni, 2002). This happens through the involvement of separate neural processes for goal-directed vs. habitual behavior (Balleine & Dickinson, 1998). Two distinct cortical-subcortical circuits are thought to be involved in the motor skill acquisition: one is the cortico-striato-thalamo-cortical loop and the other is the cortico-cerebello-thalamo-cortical loop (Middleton & Strick, 1997). Different studies have been used to support the involvement of the two cortical-subscortical circuits in motor skill learning including, lesion experiments, neurophysiological and morphological studies and investigations using neuroimaging techniques. The role of neural plasticity associated with experience and motor learning will be described in the following section.

Motor learning and plasticity

Synaptic connections and neuronal organization in the brain underlie behavior. Changes in the brain could result in a change in behavior and vice versa. Neural plasticity refers to the ability of the nervous system to change adaptively to internal and/or external environmental alterations (Liu & Wang, 2001). Such changes can be studied in different ways, from global measures of brain activity to study the changes at molecular level (Kolb, Teskey, & Gibb, 2010). To investigate the relationship between changes in the brain and that of the behavior, scientists link such changes using anatomical such as cell morphology and connectivity, physiological such as cortical stimulation, and *in vivo* imaging techniques (Kolb, Teskey, & Gibb, 2010).

Wide variety of experiences can change the brain, including sensory and motor experience, learning a task, gonadal hormones, psychomotor stimulant drugs, neurotrophic factors, electrical stimulation, stress, rewards, diet, and aging (Kolb, Teskey, & Gibb, 2010). Neural plasticity occurs through reorganization of existing circuits and/ or creating new circuits. Also, regenerating new tissue which take place after brain damage is considered as another mechanism in neural plasticity. Neural plastic alterations are not only time-dependent and change over time but also age-dependent (Kolb, Gorny, Li, Samaha, & Robinson, 2003; Kolb, Teskey, & Gibb, 2010). In addition, plasticity induced by different experiences can interact with each other. For example, drug experiences prior to brain injury may influence both spontaneous recovery and the effectiveness of postinjury treatments (Kolb, Teskey, & Gibb, 2010).

Although earlier studies of motor learning were more focused on changes in neuronal activity related to a simple reflex adaptation (Lisberger & Pavelco, 1988; Thompson, 1990), recent studies have been trying to investigate brain functional and anatomical changes associated with motor learning of more complex behaviors such as skills. These studies revealed robust functional (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Karni et al., 1995, 1998; Ungerleider, Doyon, & Karni, 2002), physiological (Greenough, Swain, Kleim, & Weiler, 1996; Hess & Donoghue, 1996; Nudo, Plautz, & Milliken, 1997; Teskey et al., 2007) and anatomical (Greenough, Larson, & Withers, 1985; Kleim, Barbay, & Nudo, 1998; Kolb, Buhrmann, McDonald, & Sutherland, 1994; Withers & Greenough, 1989) changes associated with the acquisition of a novel motor task within motor-related brain areas.

Motor skill acquisition induces synaptic plasticity and causes reorganization of movement representations within the motor cortex. The functional reorganization of movement representations has been demonstrated using intracortical microstimulation (ICMS). For example, Nudo and colleagues (1996) showed an expansion of digit representation in the primary motor cortex of squirrel monkeys associated with training on a small object retrieval task. Similarly, Kleim and colleagues (2008) demonstrated an expansion of wrist and digit representations in the caudal forelimb area of the rats trained to perform skilled reaching movements for food and they did not find such reorganization of the movement representations in the unskilled reaching rats.

Neural imaging techniques such as fMRI and PET have allowed scientists to follow dynamic neural changes that occur during different phases of motor learning. Recent findings using fMRI techniques on learning of a motor sequence such as sequential finger movements suggest that the development of skill acquisition is associated with: (1) slowly evolving functional reorganization in the primary motor cortex over several weeks, (2) this motor-activity-evoked signal changes in the primary motor cortex follows more dynamic and fast changes in the cerebellum, striatum, and other cortical areas related to motor behavior over several days. The imaging data also suggest that extensive practice of the same sequential movements results in a gradually evolving and more extensive representation of the movements in the primary motor cortex (Ungerleider, Doyon, & Karni, 2002). It has been shown that the cerebellum is active during initial training, which is the fast phase of motor learning (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Ungerleider, Doyon, & Karni, 2002), but this activity declines with more practice and it might become undetectable with over-learning (Grafton, Woods, & Mike, 1994; Ungerleider, Doyon, & Karni, 2002). Also, an increase in striatal activity can be observed with more practice of sequential movements when movements become "automatic" (Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Ungerleider, Doyon, & Karni, 2002).

The neural correlates of functional reorganization have been demonstrated mostly in the primary motor cortex. Donoghue and colleagues (1996) showed that primary motor cortex plasticity depends on horizontal connections throughout the entire region, especially in layers II/III and V within the primary motor cortex. Synaptic modification as a rapid cortical plasticity can be modulated via NMDA receptors within the involved horizontal circuitry (Nudo, Plautz, & Milliken, 1997; Sanes & Donoghue, 2000) and persistent alterations in the efficacy of the circuit results from synaptic changes through long-term potentiation (LTP) and long-term depression (LTD) mechanisms (Rioult-Pedotti & Donoghue, 2002). The synaptic mechanisms of LTP/LTD are thought to up-/ down-regulate the strength of the connections (Abraham & Bear, 1996; Hess, Aizenman, & Donoghue, 1996).

High-frequency stimulation and low-frequency stimulation have been shown to reliably induce LTP and LTD, respectively in many different areas such as the lateral amygdala (Rogan, Stäubli, & LeDoux, 1997), subthalamic nucleus (Shen, Zhu, Munhall, & Johnson, 2003), hippocampus (Saucier & Cain, 1995), visual cortex (Hager & Dringenberg, 2010), olfactory cortex (Roman, Truchet, Marchetti, Chaillan, & Soumireu-Mourat, 1999), and sensorimotor cortex (Froc, Chapman, Trepel, & Racine, 2000; Monfils, VandenBerg, Kleim, and Teskey, 2004; Teskey et al., 2007). For example, Monfils and colleagues (2004) found that increase in the synaptic efficacy through induction of LTP cause an expansion in the movement representations and dendritic hypertrophy in layers III and V of rat sensorimotor cortex. In addition, Teskey and colleagues (2007) demonstrated that induction of LTD results in smaller movement representations, a reduction in the density of excitatory perforated synapses, and an increase in the density of inhibitory synapses in layer V of rat sensorimotor cortex.

Consistent with functional and physiological reorganization in the motor cortex, structural changes also have been reported in association with motor skill learning.

According to Greenough and colleagues (1985) pyramidal cells in the motor cortex of rats trained on skilled reaching task showed a hypertrophy in the dendritic arborizations relative to those of rats without training. Also, a significant increase in the number of synapses per neuron within layer II/III of the motor cortex has been reported in rats trained on a complex motor task compared to both active and inactive ones (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996). Similarly, an increase in the number of synapses per Purkinje cell has been found in the cerebellar cortex in rats trained on a complex motor task compared to both active and inactive ones (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Kleim, Ballard, Vij, & Greenough, 1995).

Motor skill learning induces alterations in cortical connectivity by changing the range of synaptic efficacy (Martin & Morris, 2001). An increase in synaptic responses in the motor cortex associated with motor skill learning (Friedman, Rioult-Pedotti, & Donoghue, 1997; Woody, Gruen, & Birt, 1991) is an example of such alteration. The study conducted by Monfils and Teskey (2004) indicated a relation between the acquisition of a motor skill and synaptic plasticity in the sensorimotor cortex of the rat. They found that the increase in skilled reaching task proficiency induced an increase in synaptic efficacy on the contralateral side to the reaching forelimb.

However, rules of the neural plasticity are specific for each region of the brain and motor learning can be correlated with multiple opposing morphological changes even in the same region of the brain. The cell morphology measures such as dendritic length and spine density can vary independently and sometimes in opposite direction in response to the same experience (Kolb, Cioe, & Comeau, 2008; Kolb, Teskey, & Gibb, 2010; Comeau, McDonald, & Kolb, 2010). For example, an initial transient increase in dendritic length has been reported in prefrontal cortex in response to experience in an enriched environment, which has been disappeared after 2 weeks. In contrast, although no changes have seen in the sensory cortex at the beginning of the experience but a permanent changes in this region has reported after 2 weeks (Comeau, McDonald, & Kolb, 2010).

Similar results have been reported in physiological studies. Kindling as a model of brain sensitization is used for demonstrating neuronal plasticity. Repeated electrical stimulation to a specific brain site causes the progressive enhancement of seizure in the brain, which refers to kindling (Teskey, 2001). Similar to other models of sensitization, the development and expression of kindling is associated with dynamic structural plasticity such as dendritic arborization and spine density in the involved brain areas. Teskey and colleagues (2006) have reported changes in opposite direction in dendritic length and spine density of the layer III and V pyramidal neurons in a time point of 3 weeks. They demonstrated an initial reduction in dendritic length and spine density in layer III of pyramidal neurons after the cessation of seizures, which was followed by a rebound and increase in 3 weeks. These scientists also showed the same changes but in the opposite direction in the layer V pyramidal neurons with an initial increase of dendritic length and spine density followed by decrease in those measures (Teskey, Monfils, Silasi, & Kolb, 2006).

Neuroplasticity and brain damage

Behavioral scientists try to map normal behavioral and psychological functions onto specific neuronal circuits. They use variety of methods to manipulate brain tissue to demonstrate that neuronal alterations may result in changes in behavioral and psychological functions through the cause-effect mechanisms (Szechtman & Eilam, 2005; Teitelbaum & Pellis, 1992). Lesions, which damage brain tissue, are one of the oldest methods used to localize particular function to a specific region of the brain. This section will describe studies that have examined neuroplasticity from the perspective of a lesion approach.

The earliest lesion study on cortical control of skilled reaching conducted by Peterson and Francarol in 1951. They found that the motor cortex is the most effective region of the brain for handedness (Peterson & Francarol, 1951). Another early investigation on skilled reaching using motor cortex lesion conducted by Castro in 1972. Although he could not document digit use deficits directly, he argued that motor cortex injury causes digit use impairments.

Subsequently, many investigations have examined the importance of motor cortex for skilled reaching and confirmed its contribution (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Gharbawie, Gonzalez, & Whishaw, 2005; Metz, Antonow-Schlorke, & Witte, 2005; Whishaw, 2000; Whishaw, Pellis, Gorny, & Pellis, 1991). It has been found that both the rostral and the caudal forelimb areas of the motor cortex contribute to skilled reaching (Hall & Lindholm, 1974; Hyland, 1998; Gharbawie, Karl, & Whishaw, 2007; Neafsey & Sievert, 1982). Research findings on the role of the motor cortex in skilled reaching performance will be summarized in two sections in the following, behavioral outcome and recovery of function after motor cortex injury, and synaptic plasticity following the motor cortex damage.

Several factors contribute to the behavioral outcome after motor cortex injury, including stroke type (Alaverdashvili, Moon, Beckman, Virag, & Whishaw, 2008; Voorhies & Jones, 2002; Woodlee et al., 2005), infarct size and location (Gonzalez & Kolb, 2003; Whishaw, 2000), age (Brown, Marlowe, Bjelke, 2003; Sutherland, Dix, & Auer, 1996), sex (Gargano & Reeves, 2007; Zalihić, Markotić, Zalihić, & Mabić, 2010), and genetic susceptibility (Carr et al., 2002; Waters & Nicoll, 2005).

Damage to the forelimb regions of the motor cortex regardless of the type of lesion results in an acute period of depression in motor behavior especially skilled actions such as skilled reaching (Biernaskie, Szymanska, Windle, & Corbett, 2005; Erickson, Gharbawie, & Whishaw, 2007; Teskey, Flynn, Goertzen, Monfils, & Young, 2003; Whishaw, 2000; Whishaw, O'Connor, & Dunnett, 1986; Whishaw, Pellis, Gorny, & Pellis, 1991). Animals may make no reaching attempts using their contralateral to lesion limb during initial period after motor cortex injury. This acute post-injury period is considered as a state of shock or diaschisis, which could be lasted from hours to several days (Erickson, Gharbawie, & Whishaw, 2007; Gharbawie & Whishaw, 2006). Diaschisis is a distinctive stage, in which brain regions associated with the damaged area are functionally shut down and after a short time of neural and behavioral depression, recovery of function are mediated (Von Monakow, 1914).

Another distinctive feature following motor cortex injury is the strong tendency of the animals to switch their limb use for skilled reaching (Castro-Alamancos & Borrell, 1993; Peterson & Francarol, 1951; Whishaw, O'Connor, & Dunnett, 1986). When animals are restrained from switching their limb use to the ipsilateral to lesion limb, with the use of contralateral to lesion limb (bad limb) the ability to reach start to recover (Whishaw, 2000).

The first few days after the motor cortex injury the animals make very few reaching attempts and successes but over the course of 14 days their reaching attempts and successes start to increase (Gharbawie, Gonzalez, & Whishaw, 2005; Whishaw, 2000). Although the total success rate almost recovers to the preoperative levels using compensatory movements, this recovery occurs with a dramatic increase in reaching attempts. Many more reaching attempts are needed for an animal to make a successful reach. In addition, the single reach success scores are extremely poor and never recover (Gharbawie & Whishaw, 2006; Whishaw, Alaverdashvili, & Kolb, 2008). Therefore, post-operative recovery is incomplete with very poor single reach success, too many reaching attempts, and almost regaining the pre-operative level of successful reaching with the use of compensatory movements such as the substitution of body rotation for lost or abnormal movement elements including aim, advance, pronation, supination and release (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Gharbawie, Gonzalez, & Whishaw, 2005; Metz, Antonow-Schlorke, & Witte, 2005; Whishaw, Pellis, Gorny, & Pellis, 1991).

Considerable works show the involvement of the motor cortex in both the learning and performance of skilled reaching (Gharbawie & Whishaw, 2006; Kleim et al., 2002, 2004; Monfils & Teskey, 2004; Rioult-pedotti, Friedman, Hess, Donoghue, 1998; Whishaw, 2000; Whishaw, O'Connor, & Dunnett, 1986; Withers & Greenough, 1989). It has been shown that there are similar stages for the acquisition of skilled reaching and recovery after motor cortex damage.

Three oppositions are learned sequentially before and after motor cortex stroke. These oppositions are invariant relationships between a body part and food target but they can be achieved with variable movements. These relationships consist of a snout-food pellet opposition, which organizes the movements of orienting, a hand-food pellet opposition, which organizes the limb transport and grasping movements, and a mouth-food pellet opposition, which organizes the limb withdrawal and release movements. These oppositions are disrupted after the motor cortex injury and reestablished during recovery in the same order in which they were acquired prior to the damage (Gharbawie & Whishaw, 2006). Although regaining of the oppositions after the motor cortex injury are similar to the acquisition prior to the damage but the movements used are not normal and rats use compensatory movements such as trunk rotation and head movements to complete the task (Whishaw, Alaverdashvili, & Kolb, 2008).

It is assumed that behavioral changes and functional compensation following the motor cortex damage are associated with plastic changes in synaptic connections and neuronal organization underlying the behavior. A cascade of molecular and cellular changes evolves after brain injury in the related regions. For example, degenerative processes occur during first few days after brain damage in which cell death and atrophy of synapses can be observed. After the stabilization of degenerative processes, a slow development of new sprouting of remaining motor system pathways occurs over time (Gonzalez & Kolb, 2003; Kolb, Teskey, & Gibb, 2010). Thus, the organization of cerebral cortex changes because of the neuronal loss and disruption of neural circuits connected to the damaged area (Nudo, Barbay, & Kleim, 2000). This neural reorganization occurs at different levels of the nervous system, including the cortical regions, red nucleus, cerebellum, and spinal cord (Butefisch, 2006).

Neural reorganization can take place either in the injured hemisphere and/or in the intact hemisphere following motor cortex injuries. It has been shown that following sensorimotor cortex lesion in rats an initial atrophy on dendritic field of pyramidal neurons take place followed by sprouting and increase in dendritic branching which is correlated with recovery of performance (Kolb, 1995; Kolb, Cioe, & Whishaw, 2000). Also, It has been shown that following unilateral motor cortex damage in rats some contralesional changes occur in the intact hemisphere, including increased dendritic arborization and synaptogenesis (Adkins, Voorhies, & Jones, 2004; Biernaskie & Corbett, 2001; Jones, 1999; Jones, Kleim, & Greenough, 1996). However, a recent study has shown a reduction in dendritic arborization in both cortical hemispheres, which were reversed by complex housing (Witt-Lajuenesse, Cioe, & Kolb, in press). The contradictory findings might be related to lesion etiology, lesion size, and experience (Whishaw, Alaverdashvili, & Kolb, 2008). Gonzalez and Kolb (2003) compared different lesion etiologies and found although the behavioral outcomes of all types of lesions were similar, the structural plasticity varied with the lesion etiology and location of cells. They found opposite dendritic changes in layer V pyramidal neurons in the intact hemisphere after two types of lesions, an increase in dendritic length after injuries via devascularization and a decrease in dendritic length after aspiration injuries. Also, they found an increase only in the spine density following aspiration.

Examination of other cortical and subcortical regions such as medial prefrontal cortex and striatum showed that lesions made with devascularization led to bilateral increase in dendritic arborization in layer III pyramidal neurons in the Cg3 whereas an opposite change was found after aspiration injuries. Although they did not find any structural modifications in the Cg3 after middle cerebral artery occlusion but they found bilateral increase in dendritic length in the striatum (Gonzalez & Kolb, 2003).

It is clear that the recovery of function and structural plasticity after motor cortex damage are associated with experience. Investigators use behavioral rehabilitation to promote structural plasticity and functional recovery. One of the effective methods of treatment is complex housing (Biernaskie & Corbett, 2001; Johansson, 1996; Kolb & Elliot, 1987). It has been found that motor skill improvement after motor cortex injury is correlated with experience-induced plasticity such as enhancement of dendritic length and spine density in both intact and injured cortex (Biernaskie & Corbett, 2001; Johansson & Belichenko, 2002; Kolb & Elliot, 1987). But this functional and structural improvement is time-dependent (Biernaskie, Chernenko, & Corbett, 2004). Biernaskie and colleagues (2004) found that complex housing can be more effective if is provided earlier after brain damage and thus the functional improvement is correlated with structural plasticity. Taken together, structural plasticity and functional recovery after motor cortex damage vary with the region of study, the type of lesion and that of experience, age and other factors (Biernaskie & Corbett, 2001; Gonzalez & Kolb, 2003; Kolb & Elliot, 1987; Kolb, Cioe, & Whishaw, 2000; Kolb & Teskey, 2010). Thus, more detailed investigations are required for understanding the relations.

In conclusion, the present introduction was an attempt to put together the most relevant variables that play crucial roles in understanding reaching behavior as our model in studying individual differences in rats as simpler animals in the hierarchy of evolution.

Such approach will enhance our chance to examine individual differences in a more controlled and systematic manner. Although, the neural organization of brain have not been directly examined in the present thesis, it is presumed that individual differences in skill reaching in rats is perhaps somewhat mediated by such reorganization in neural circuits explained in the first part of this introduction as they have been recognized as relevant to the motor behavior.

Objectives of the thesis

The present thesis attempted to accomplish two goals. The first is to characterize individual differences in skilled reaching for food in the rats by providing in depth descriptions of such differences. The second is to find potential sources underlying the differences by examining the brain. The experiments focused on individual differences because such investigation provides valuable insights into the evolution, development and learning of motor skills and also helps optimizing preventative and therapeutic care for individuals.

The goals of the study were achieved by two sets of experiments. In the first phase of the investigation, experiments were designed to assess skilled reaching performance in normal animals during the acquisition and asymptote period of the skill. In these subjects, possible relations between individual differences and other behavioral characteristics and neurobiological differences in the brains were examined. In the second phase of the study, the potential sources underlying the differences and the distribution of individual differences were examined under two different methods of brain manipulation. The first induced behavioral sensitization by repeated exposure to psychomotor stimulant drugs. In the second, the relationship between individual differences in performance and motor cortex damage were examined. Taken together the thesis had four objectives.

Objective 1: Individual differences in skilled reaching for food related to increased number of gestures

In this study, individual differences in skilled reaching for food in rats were documented through series of behavioral and anatomical experiments. Rats were trained in single pellet reaching task and their reaching performances were analyzed using three different evaluation methods: endpoint measures, kinematic analysis using a scale derived from Eshkol-Wachmann Movement Notation (EWMN), and gesture analysis. The variability in their reaching performances was explored in relation to motor ability, general motor activity, rehabilitation, and gross anatomical measures including brain weight, cortical thickness, Acetylcholinesterase density, number of cells in the motor cortex, and pyramidal tract size.

Objective 2: Individual differences in skilled reaching for food emerged with practice

In this study, the development of skilled reaching during skill acquisition period was examined and learning curves for animals with good and poor reaching skills were assessed to investigate individual differences skill acquisition. Skilled reaching in rats was monitored from the beginning of the skill acquisition until it reached asymptote. Reaching performance was analyzed in terms of endpoint measures and kinematic analysis during several stages of the skill learning. This in depth investigation of the individual differences was designed to obtain an estimate on the rate of the skill acquisition in animals that end up displaying either poor or good reaching ability.

Objective 3: Individual differences related to brain changes induced by sensitization with amphetamine or nicotine

Two experiments explored the effects of behavioral sensitization on the subsequent acquisition of skilled reaching. In the first experiment, animals were trained following a regime of sensitization with amphetamine. In the second experiment, animals were trained following a regime of sensitization with nicotine. Both drug treatments produce widespread structural changes in the brain and so provide a possible manipulation that might expose the neural origins of individual differences in motor performance.

Objective 4: The relation between individual differences and motor cortex damage

The final experiment examined the effects of small motor cortex lesions on the display of individual differences in skilled reaching. Rats were trained on the single-pellet reaching task prior to the motor cortex damage. Then, they were received consistent small motor cortex lesions in the caudal region of the forelimb area on the contralateral side via pial strip procedure. The reaching abilities were assessed using endpoint measures and kinematic analysis for 3 weeks, which was started 24 hours after the surgery. Then brains were harvested, sectioned and stained to visualize the location of the lesions for measurements. The expectation was that rats would show different rates of recovery following damage to the motor cortex that were related to individual differences prior to the injuries.

CHAPTER 2

Individual differences in skilled reaching for food related to increased number of gestures: Evidence for goal and habit learning of skilled reaching

Modified from a paper published in _Behavioral Neuroscience,_ 123(4): 863-874 by Gita Gholamrezaei and Ian Q. Whishaw in 2009.

Abstract

Reaching for food with a forelimb by the rat (skilled reaching) is widely used as a model for neurobiological studies of motor function and for the study of abnormalities associated with acquired nervous system disorders in humans. Although many aspects of the motor act of reaching in rodents and primates are similar, success in reaching by rodents is distinctively variable but the source of this variability has not been examined previously. Long-Evans rats were video taped as they reached for food in two different reaching tasks and end-point measures of performance were examined in relation to variables previously associated with individual differences including: (1) testing procedures and rehabilitation, (2) movement ability, (3) general locomotor activity, and (4) cortical anatomy (brain weight, cortical thickness, Acetylcholinesterase density, number of neurons in motor cortex, pyramidal tract size). There were striking and consistent individual differences in performance but these were not related to the dependent measures related to training, movement ability, locomotor activity or anatomy. Success was negatively related to numbers of gestures (non-weight bearing movements of the reaching limb) used on a reach, however. The results are discussed in relation to the idea that individual differences in response strategy bias some rats to use a goal strategy and others to use a habit strategy for skilled reaching.

Introduction

Individual differences are universally expressed in animals (Darwin, 1859) and contribute to many different experimental investigations in behavioral neuroscience (Anastasi, 1965; Cooper, 1998). Individual differences are manifest even in relatively inbred strains of laboratory animals (Anderson, 2000; Mormede et al., 2002). Furthermore, they can be measured in all behaviors including learning and memory (Hooks et al., 1994; Topic et al., 2005), ageing (Rapp & Amaral, 1992), reactivity to novelty (Antoniou et al., 2008; Dellu, Piazza, Mayo, Le Moal, & Simon, 1996; Thiel, Muller, Huston, & Schwarting, 1999), response to reward (Flagel, Watson, Akil, & Robinson, 2008; Tonissaar, Herm, Rinken, & Harro, 2006), emotion (Clinton, Miller, Watson, & Akil, 2008; Ho, Eichendorff, & Schwarting, 2002) and scheduled induced behavior (Mittleman & Valenstein, 1985). Individual differences have also been used for the selection of animal strains as models for such psychiatric disorders as addiction (Ellenbroek, van der Kam, van der Elst, & Cools, 2005; Spanagel, 2000), attention deficit/hyperactivity (Viggiano, Vallone, Ruocco, & Sadile, 2003), emotion and learning (Blizard & Adams, 2002; Innis, 1992).

Individual differences are also present in motor skills (Buitrago et al., 2004), including fine motor skills such as human reaching for and grasping objects (Wong & Whishaw, 2004). Anecdotal reports suggest that there are also individual differences in rat skilled reaching for food (Peterson & Fracarol, 1938; Whishaw & Kolb, 2005). Individual differences in rat skilled reaching pose a special opportunity and challenge for behavioral neuroscience. Theoretically, individual differences can provide insights into the evolution (Nikkhah, Rosenthal, Hedrich, & Samii, 1998; VandenBerg, Hogg, Kleim,

& Whishaw, 2002; Whishaw, Gorny, Foroud, & Kleim, 2003), development (Greenough, Black, & Wallace, 1987; Kolb & Gibb, 1991), and learning (Hermer-Vazquez, Hermer-Vazquez, & Chapin, 2007; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Nudo, 2006) of motor skills. Practically, as rat skilled reaching is widely used to model human neurological conditions, variability in the normal performance of the rats intrudes upon the interpretation of impairments produced by neurological manipulations (Adkins, Boychuk, Remple, & Kleim, 2006; Döbrössy & Dunnett, 2006; Girgis et al., 2007; Jones, Chu, Grande, & Gregory, 1999; Kleim, Jones, & Schallert, 2003; Kolb, Cioe, & Whishaw, 2000; MacLellan, Gyawali, & Colbourne, 2006; Teskey et al., 2007; Whishaw, Alaverdshvili, & Kolb, 2008). Surprisingly, although individual differences in skilled reaching manifest in many studies, their source has not been systematically examined. This deficiency is addressed in the present study.

The present experiments had three objectives. First, because individual differences in rat skilled reaching have not been systematically described and related to task acquisition/rehabilitation, performance across trials and days of training is described. Long-Evans rats were used because performance of this strain in the skilled reaching task has been standardized in previous research (Whishaw et al., 2002). Second, because individual differences could potentially be caused by abnormalities in limb use, success was related to limb movement scores derived from frame-by-frame video movement assay as described with Eshkol-Wachmann Movement Notation (EWMN) (Eshkol & Wachmann, 1958), which describes movement elements (Whishaw & Pellis, 1990), and Laban Movement Analysis (LMA) (Laban, 1971), which describes gestures (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Foroud & Whishaw, 2006). Third, because individual differences have previously been associated with a propensity to show heightened general activity (Davis, Clinton, Akil, & Becker, 2008; Piazza, Deroche, Rouge-Pont, & Le Moal, 1998), as well as gross anatomical features of the cortical motor system such as preexisting stroke or injury or abnormalities such as cortical warts (Sherman, Galaburda, & Geschwind, 1985), performance was related to locomotor activity and to anatomical measures of the cortical motor system including brain weight, motor cortical thickness, Acetylcholinesterase (AChE) intensity in motor cortex, number of cells in the caudal forelimb motor area, and pyramidal tract size (Juraska, 1991; Kolb & Whishaw, 1998; Greenough, Larson, & Withers, 1985).

Method

Subjects

Twenty adult (120 days old, weight 256-334 g) female Long-Evans hooded rats raised at the University of Lethbridge vivarium were used. They were housed as pairs in standard Plexiglas cages in an animal colony room with a 12h light-dark cycle (lights on 7:30-19:30h) with temperature maintained at 22 °C. The experiments were approved using the guidelines of the University of Lethbridge animal care committee and the Canadian Council for Animal Care, which complies with international standards for animal care.

Feeding

Rats were food deprived to 85-90% of their normal body weight prior to the beginning of experiments. Each rat received 15g of Purina rat chow once a day to maintain at that body weight. The rats also received 0.9g of 45mg dustless precision banana-flavored pellets (product #F0021, Bioserve Inc., Frenchtown, NJ, USA) for 3 days prior to initial training on the single pellet-reaching task to familiarize them with the taste and smell of the food. During training and the experiments, the banana-flavored pellets were served as targets in the reaching task. Each rat could receive up to 20 pellets per day depend on the animal's reaching accuracy.

Reaching apparatus

Two different types of reaching apparatus were used in this study: single pellet reaching box and food tray box (Whishaw, O'Connor, & Dunnett, 1986; Whishaw & Pellis, 1990).

Single pellet reaching box

The single pellet-reaching box is made of transparent Plexiglas with 45 cm length, 14 cm width, and 35 cm height. In the middle of the front wall, a 1 cm wide slit is extended from bottom of the box to a height of 15 cm. A 2 cm wide by 4 cm long shelf is attached to the outside of the front wall, 3 cm above the bottom of the box in front of the opening. There are two small indentations with 1.5 cm distance from the front wall aligned with each side of the slot to hold the food pellets. A food pellet in each indentation is accessible only to the contralateral hand, because it pronates medially to grasp.

Food tray box

The Food tray boxes measured 10 cm long, 18 cm wide, and 10 cm high. The tops, backs, and sides of the boxes are made of transparent Plexiglas. The front of the box is constructed of 2 mm bars that are separated by 9 mm distance. A 4 cm wide and 5 mm deep tray mounted in front of each box and extended for the length of the box, serves to contain granules of food (20-40 mg chick feed). The floor of the boxes is made of metal grids, so that dropped chick food would not be accessible to a rat.

Reach training

Each animal was handled for 5 min on 5 consecutive days prior to the training and also each received twenty food pellets for 3 days before training began. Reach training was conducted in a different room from that used to house the animals. Training sessions took place every day at the same time.

Single pellet reaching task

Rats were trained in the single pellet-reaching task for 14 days. Training consisted of several steps:

(1) *Apparatus habituation*. Naïve animals were placed in the reaching apparatus individually for 10 min sessions daily. The objective was to introduce the rat to the reaching box with pellets on the shelf and to have the rat retrieve the pellet by hand or tongue. Once a rat was successfully retrieving the pellets, by moving the food pellets further away on the shelf, it was encouraged to use a hand to retrieve the food.

(2) *Establishing hand dominance*. To determine the dominant forelimb, initially pellets were presented in both indentations. Once a rat showed a clear preference for one hand, by making more reaching attempts with it, the food pellets were presented in the indentation contralateral to the dominant hand.

(3) *Full sequence reaching*. To obtain discrete reaching trials, the rat’s behavior was shaped to leave the slot, walk to the rear wall of the box, turn, and approach the slot again for the next pellet. Thus, a rat was required to reposition its body for each reach. In addition, by withholding food on semi-randomly selected trials, rats were taught to sniff

the shelf for a pellet and to reach only if a pellet was present (Alaverdashvili, Foroud, Lim, & Whishaw, 2008). Single pellet reaching tests were performed for 5 consecutive days after the completion of the training sessions. Each testing sessions consisted of 20 trials.

Food tray task

Rats were placed in the reaching boxes for 1 hour daily for 10 consecutive days for training. In this task, a rat had to reach through the bars, grasp the food granules and retract the hand with the food. If a rat dropped the food granules, the food was lost and the rat had to reach for food again. Food tray reaching performance was measured for 2 consecutive days after the completion of the training sessions. A rat's reaching performance was video recorded for 5 min in each testing sessions.

Single pellet reach retraining

Rats were retrained in the single pellet-reaching task for ten more days and their reaching movements were recorded. Each session consisted of 20 trials.

Open field

Locomotor activity was measured in a transparent Plexiglas box 42 cm length, 24 cm width, and 30 cm height monitored by Versamax animal activity monitoring system (AccuScan Instruments, Inc.). Open field activity was measured for 10 min on five consecutive days. Total distance traveled was used as the dependent measure of activity.

Video recording

Video records were made with a Sony 3CCD camcorder with a shutter speed of 1000th of a second. Illumination for high shutter speed filming was provided by a cold light source (Whishaw & Pellis, 1990). Frame by frame analysis was done at 30 frames per second using a Sony digital videocassette recorder DSR-II. Representative still frames were captured from digital video recordings with Final Cut Pro HD (V.4.5 http://WWW.apple.com).

Behavioral analysis

Endpoint measures

Reaching performances were analyzed in each trial for the number of attempts, first reach success, and total success (Whishaw & Kolb, 2005; Whishaw, Pellis, & Gorny, 1992).

Trial. On each trial the rat had to approach the slot from the back of the box, reach for the food pellet through the slot, and after attempting to gain the food, return to the rear of the box. Once a rat was trained, a trial was typically associated with the rat grasping the food or else knocked it off the shelf.

Attempt. A reach attempt is defined as a forward movement of rat's preferred forelimb through the slot in the front wall of the reaching box in an attempt to grasp and obtain the food. A reach attempt could be successful or not. All reach attempts were recorded for each trial and session.

First reach success. First reach success is defined as a reach attempt in which the food pellet is grasped with the first advance of the forelimb and is consumed by the rat. First reach success percent was calculated by the following formula:

First reach success (%) = (Number of first reach successes/ Number of trials) × 100

Total success. All reaches made by the rat that resulted in obtaining food with the hand, despite the number of reach attempts, are defined as successes. Total success percent was calculated by the following formula:

Total success (%) = (Number of successes/ Number of trials) × 100

Movement element analysis

Movement element analysis was performed using a rating scale derived from Eshkol-Wachmann Movement Notation analysis of reaching (Eshkol & Wachmann, 1958). This conceptual framework is based on the analysis of the relations and changes of relations between parts of the body. Ten reaching elements were analyzed and scored for first three successful reaches and a mean was calculated. Ten reaching elements were defined as:

(1). Digits to the midline. The reaching limb is lifted from the floor so that the tips of the digits are aligned with the midline of the body.

(2). Digits flexed. As the limb is lifted, the digits are flexed and closed, the hand is supinated and the wrist is partially flexed.

(3). Elbow in. The hand and elbow are carried inward to the midline of the body.

(4). Advance. The limb is advanced directly through the slot toward the food pellet.

(5). Digits extend. During the advance, the digits extend toward the food pellet.

(6). Arpeggio. When the hand is over the food pellet, it pronates from digit 5 through to digit 2, and at the same time the digits open.

(7). Grasp. The digits close and flex over the food pellet, with the hand remaining in place, and the wrist is slightly extended to lift the food.

(8). Supination I. As the forelimb is withdrawn, the hand supinates by almost 90°.

(9). Supination II. Once the hand is withdrawn from the slot to the mouth, it supinates further by about 45° to place the food pellet in the mouth.

(10). Release. The mouth contacts the hand and the digits open to release the food pellet.

Each of the 10 reaching elements was rated on a three-point scale to obtain movement scores. A score of “0” was given for a normal movement, a score of “0.5” was given for abnormal movement, and a score of “1” was given for the absence of the movement (Piecharka, Kleim, & Whishaw, 2005; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993).

Gesture analysis

Gesture analysis was performed using the “Expressive Reaching Scale” derived from the Laban Movement analysis Notations of reaching. This rating scale provides a method for quantifying the non-kinematic features of movement (Foroud & Whishaw, 2006). In ERS, a reaching movement consists of four gestures including: advance, grasp, withdrawal, and release (Figure 2.1). A gesture is defined as one action made by one limb or one limb segment. Four reaching gestures were defined as:

(1). Advance. The limb is advanced toward the food pellet.

(2). Grasp. The digits are closed over the food or near the food pellet.

(3). Withdraw. The hand is withdrawn toward the mouth.

(4). Release. The digits are flexed and the limb is moved away from the mouth.

The last testing session was used for determining the number of gestures. Gestures were scored on each trip made by a rat to the front of the reaching box. A score

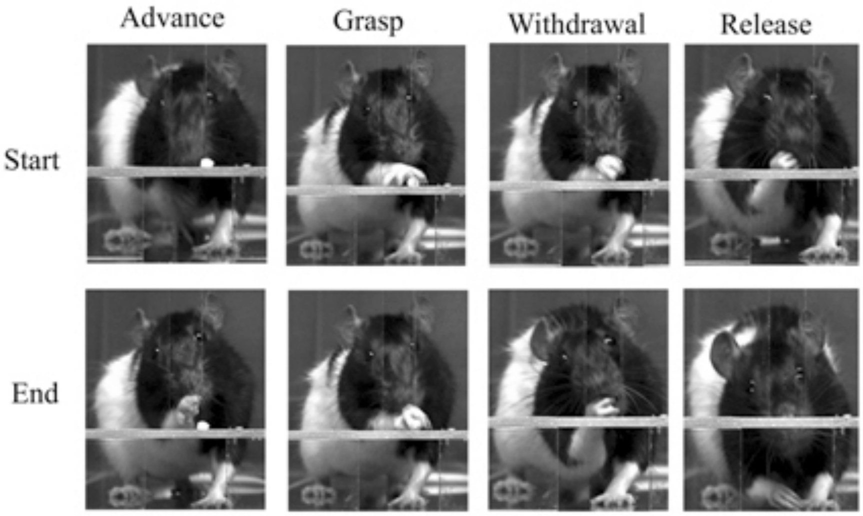


Figure 2.1. The start and finish of each of the four gestures: advance, grasp, withdrawal, and release.

of "1" was given for each gesture. A successful reach required a minimum of four gestures. A failed reach was associated with a minimum of three gestures (withdrawal to the mouth was not observed for missed reaches). Both successful and failed reaches could be associated with many additional gestures, however (Alaverdashvili, Foroud, Lim, & Whishaw, 2008).

Histology

At the completion of the behavioral experiments, rats were euthanized with an overdose of sodium pentobarbital and perfused transcardially with 0.9% phosphate buffered saline followed by 4% phosphate buffered paraformaldehyde. The brains were removed from the skull, weighed, and then post-fixed and cryoprotected in a 30% sucrose and 4% paraformaldehyde solution. The brains were then cut coronally in 40 μm sections on a freezing microtome. Twelve sets of slices were prepared. Two sets of slices were stained with Cresyl violet stain to determine cortical thickness and pyramidal tract size, and two sets of slices were stained for Acetylcholinesterase (AChE) to determine the density of the AChE activity in the motor cortex. Two additional sets of slices were stained with Fluorescent Nissl stain for the stereological analysis. Four brains (two brains from each group) had to be removed from the anatomical analysis because of inadequate tissue preparation.

Cortical thickness

Cortical thickness was measured by projecting the cresyl violet-stained sections on a Zeiss DL 1 POL petrographic projector set at a 17.5X magnification. Three measurements (medial, central, and lateral) were taken from the edge of the white matter to the outer edge of the cortex using a transparent millimeter ruler for each of the following planes; plane 1, first section with caudate putamen visible; plane 2, center of anterior commissure; plane 3, first section with a visible hippocampus; plane 4, posterior commissure; plane 5, most posterior section with a visible hippocampus. Mean thickness at each plane was calculated by averaging across each of the three measurement locations.

AChE densitometry

Digital images were captured from six different coronal sections stained with AChE stain throughout the motor cortex. An image analysis program (Scion Image 6.21, NIH, USA) was used to estimate the density of the AChE activity in the layer V of the motor cortex with the sample size of 0.16 × 0.16 inches. Two measures were taken from each hemisphere, one measure in M1 and the other in M2 (Zilles, 1985). Mean AChE density at each plane was calculated by averaging those measures.

Pyramidal tract size

Digital images were captured from three coronal sections (6 sections apart) stained with Cresyl violet stain from the largest part of pyramidal tract and the size of pyramidal tract was measured using an image analysis program (Scion Image 6.21, NIH, USA) and the mean was calculated by averaging across the three measures.

Number of cells

Two sets of brain sections (every sixth section) stained with fluorescent Nissl stain were used to quantify the total number of cells in caudal forelimb motor area using optical fractionator method with Stereo Investigator 7 software program (mbf Bioscience, MicroBright Field, Inc. Vermont, USA). A Zeiss Axio Imager M1 microscope equipped with a microcator and a motorized x-y specimen stage were used. A video camera

(Sensicam QE, the Cooke corporation, Germany) was mounted on top of the microscope and connected to a computer.

The initial delineations of the region in both hemispheres were performed using a 2.5X objective (Zeiss, EC Plan – NEO) and the sections were analyzed using 100X oil immersion objective (Zeiss, Plan Apo 1.40NA). Counts of cells were made at regular pre determined distances (between bregma and 2 mm anterior) within subdivisions with 50-55 sampling sites in each hemisphere. After delineation of each sampling side, 2D unbiased counting frames (Gundersen, Jensen, Kieu, & Nielsen, 1999) with an area of 200×200 μm were superimposed on the field of view. The thickness of the tissue was selected (32 μm) and 10 μm of guard height were considered for upper and lower surface of the section and cells in 12 μm (disector height) between guard zones were counted. The total number of cells (N) in caudal forelimb area in each hemisphere was estimated:

$$N = \frac{1}{ssf} \frac{1}{asf} \frac{1}{hsf} \Sigma Q^{-}$$

In the above formula, $\sum Q^{-}$is the total number of cells counted, ssf is the section sampling fraction, asf is the area sampling fraction, and hsf is the height sampling fraction.

Statistical analysis

The results were subject to multivariate and repeated measures analysis of variance (ANOVA). Comparisons of means between groups were performed using unpaired t-tests. To test for correlations between behavioral variables, Pearson's correlation coefficient was applied. In all statistical analyses, a *p*-value of less than or equal to 0.05 was considered significant. All results were presented as mean ± the standard error of the mean (SEM).

Results

Reaching performances were analyzed by trials (a trial was defined as an approach and reach through the slot for the food pellet, withdrawal of the limb, and return to the back of the box).

End point measures

A summary of three end point measures of skilled reaching, total success, first reach success and number of attempts are shown for each rat in Figure 2.2. The results are order on the basis of success scores. The variation of total reaching success was high between individual animals, with the highest score of 86% and the lowest score of 30%, representing an almost three-fold difference (Figure 2.2.A). Animals with high total success score also had high first reach scores (Figure 2.2.B) and a lower number of attempts (Figure 2.2.C).

The correlation between total success and first reach success was significant, r (19) = 0.85, $p < 0.01$ (Figure 2.3.A). In addition, the correlation between success scores and number of attempts were significant, (total success: r (19) = -0.58, $p < 0.01$ (Figure 2.3.B); first reach success: r (19) = -0.81, $p < 0.01$ (Figure 2.3.C).

Because each testing session consisted of 20 trials give on each of 5 days, correlational analysis was performed between each endpoint measure and trial number. Overall, the performance across trials was similar and there was no significant correlation between total success and trial number (Figure 2.4.A). Nevertheless, there was a significant positive correlation between first success and trial numbers, r (19) = 0.48, $p <$

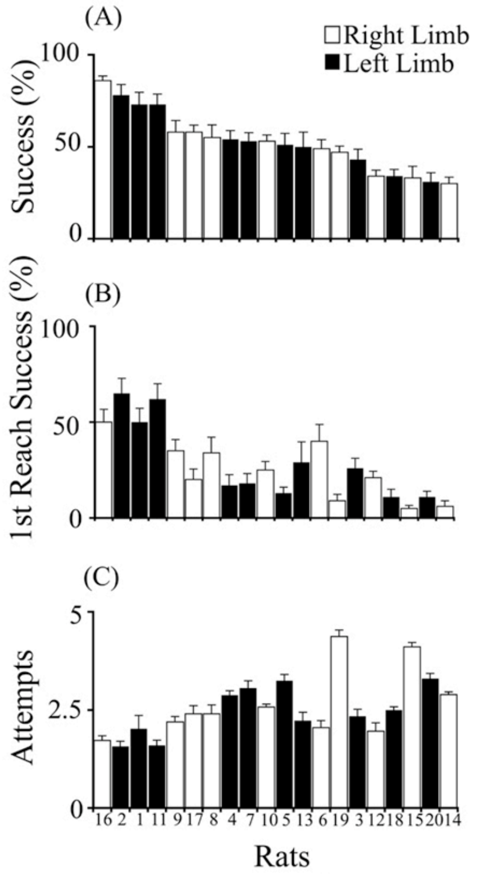


Figure 2.2. Individual skilled reaching performance (mean and standard error over 5 days). (A) total reaching success, (B) first reach success, and (C) number of attempts. Note: The rats are ordered by success scores.

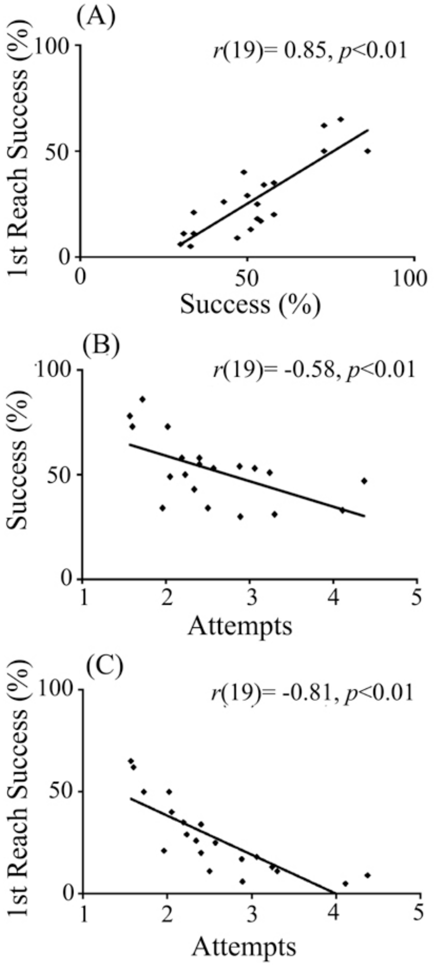


Figure 2.3. Correlation between: (A) success and first reach success, (B) success and the number of attempts, and (C) first reach success and the number of attempts.

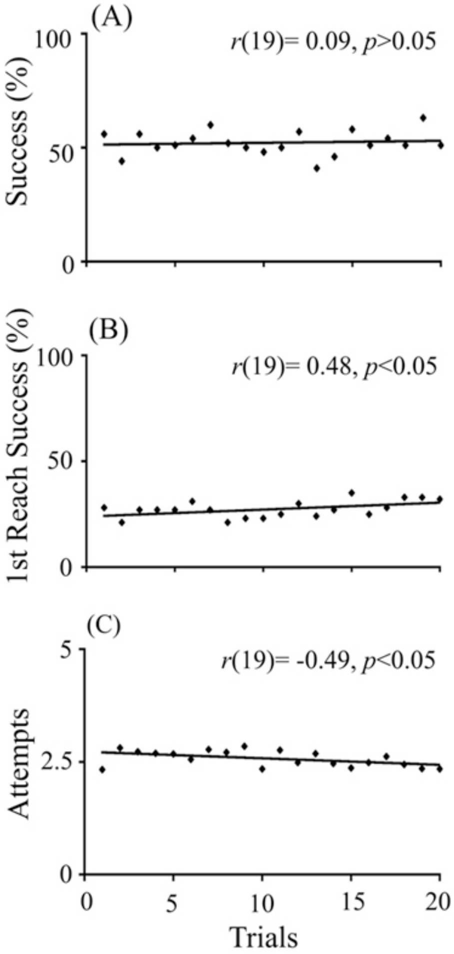


Figure 2.4. Trial-by-trial performance (mean of 5 days and correlation): (A) total success, (B) first reach success, and (C) number of attempts. Graphs represent correlation between performance and the trial number.

0.05 (Figure 2.4.B), and also a negative significant correlation between attempts and trial numbers, r (19) = -0.49, $p < 0.05$ (Figure 2.4.C).

Thus, although each rat maintained its relative performance with respect to other rats across trials, there was a tendency for the rats to make more first trial success across each test session, which reduced the number of attempts.

Movement elements

The analysis of data from EWMN rating scale indicated no significant difference between movement elements in rats reaching movements, F (1,18) = 1.43, $p > 0.05$. In general, the rats received scores of close to "0" for all movement elements, which is typical of a normal reach. Consequently, there were no significant correlations between the rats EWMN mean score and the end point measures (success: r (19) = 0.25, $p > 0.05$; first reach success: r (19) = 0.23, $p > 0.05$; attempts: r (19) = - 0.22, $p > 0.05$).

Gesture analysis

Gesture analysis and correlations showed that the number of gestures used in a trial was significantly related to reaching success. Gestures including advance, grasp, and release are negatively correlated with the success, (advance: r (19) = -0.52, $p < 0.05$ (Figure 2.5.A); grasp: r (19) = -0.47, $p < 0.05$ (Figure 2.5.B); and release: r (19) = -0.50, $p < 0.05$ (Figure 2.5.D). A positive correlation was found between the number of withdrawal and success percentage, r (19) = 0.91, $p < 0.01$ (Figure 2.5.C). Stated differently, rats displaying poor success made more of the first three gestures on each

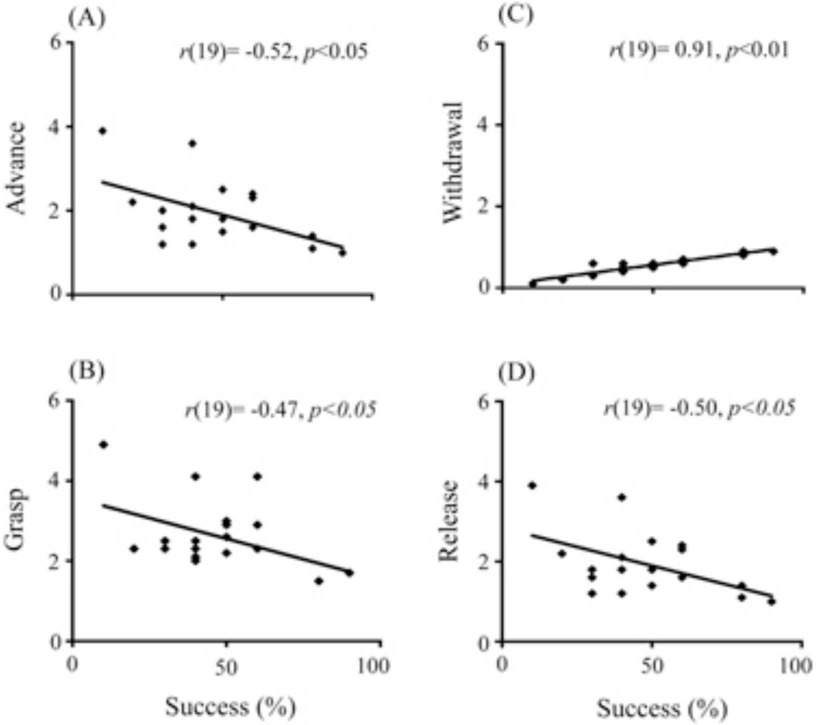


Figure 2.5. Correlation between incidence of gesture and total success: (A) advance, (B) grasp, (C) withdrawal, and (D) release.

reach, and because the obtained food less often, therefore made fewer withdrawal gestures.

Tray reaching task

The performance of rats on the tray-reaching task is shown in Figure 2.6. No relationship was found between reaching success and number of attempts. During training days, 30% of the animals (6 out of 20 rats) switched their forelimb preference and they used the single pellet task non-dominant hand for reaching.

No correlation was found between reaching success in tray task and single pellet task, $r\ (19) = -0.01$, $p > 0.05$ (Figure 2.7).

Single pellet retraining

Following tray task training, the rats were retrained in the single pellet-reaching task for 10 days. Those rats that had changed their forelimb preference in the tray task switched to the limb that they originally used in the single pellet task. Their success scores were very similar to their original performance on the task; correlations between the results from first training and the retraining in the single pellet task, $r\ (19) = 0.50$, $p < 0.05$.

Group differences

To relate activity and histological measures to reach success, the rats were divided into two groups based on reaching success scores in the original testing, thus giving a group of rats with higher success scores (HS) and a group of rats with lower success scores (LS). A repeated measure ANOVA revealed a significant difference in first reach success between HS and LS groups, $F\ (1,18) = 3.45$, $p < 0.05$ (Figure 2.8).

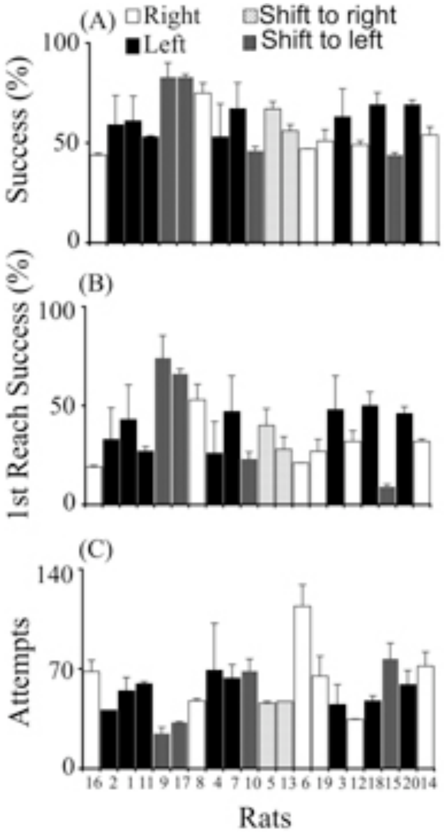


Figure 2.6. Tray task performance of individual rats (mean ± *SEM*). (A) total reaching success, (B) first reach success, and (C) number of attempts. Note: Rats are ordered in terms of success in single pellet reaching and also rats with changed limb preference from right to left are shown with less dark bars and from left to right are shown with darker bars.

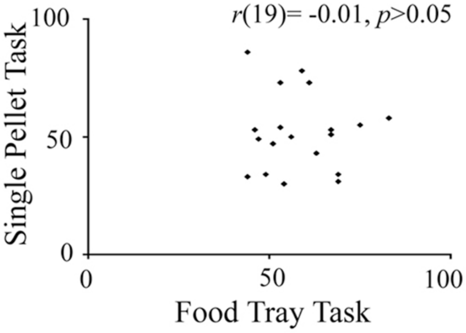


Figure 2.7. Correlation between total success on the single pellet and the tray task.

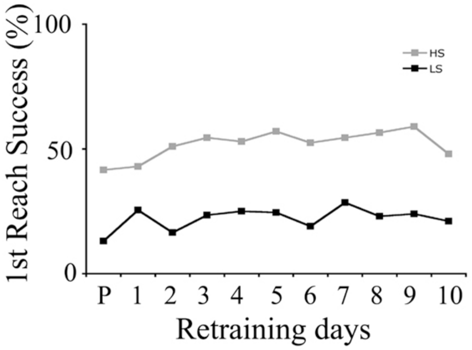


Figure 2.8. First reach success (mean) with additional training on the single pellet-reaching task in higher success (HS) and lower success (LS) groups. P = previous score at the original testing. Note: Uniform differences between groups.

Open field

Total distance traveled by rats in the open field apparatus were measured for five days and a comparison of total distance traveled between HS and LS groups did not reveal a significant difference, F (1,18) = 0.12, $p > 0.05$ (Figure 2.9). Open-field locomotion was not correlated with the end point measures (Success: r (19) = - 0.24, $p > 0.05$; First reach success: r (19) = -0.125, $p > 0.05$; Attempts: r (19) = - 0.008, $p > 0.05$).

Histology

Mean and p values for the neurobiological measures for HS and LS groups are shown in Table 2.1. A comparison of the neurobiological measures including, brain weight, cortical thickness, AChE activity of the motor cortex, pyramidal tract size and number of cells did not reveal a significant difference between groups. There was a relation between performance and hemispheric density of AChE, which was attributable to limb preference in that the AChE density in the ipsilateral hemisphere was higher than that in the contralateral hemisphere. A pairwise comparisons between groups based on handedness revealed a significant effect of AChE density for the ipsilateral hemisphere F (1,14) = 4.96, $p < 0.05$, but not in the contralateral hemisphere, F (1,14) = 0.013, $p > 0.05$ to the preferred limb.

Discussion

The objective of the present study was to investigate individual differences in a skilled motor ability in adult rats and to investigate possible relations to other behavioral characteristics and neurobiological differences in their brains. There was variability in the skilled reaching performance of the rats, with the most successful animal obtaining end

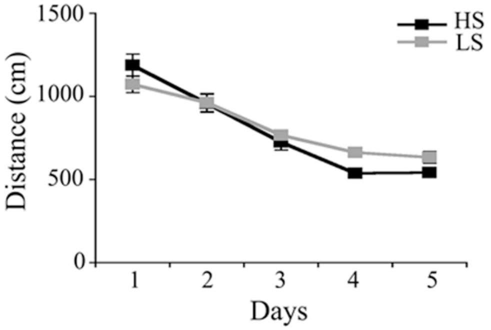
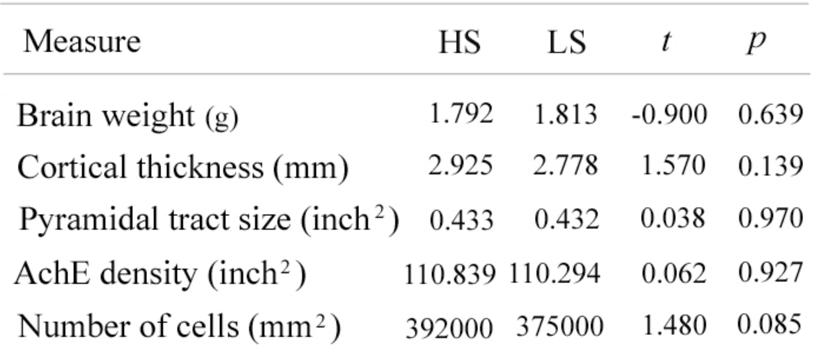


Figure 2.9. Distance traveled (mean ± *SEM*) by higher success (HS) and lower success (LS) groups over 5 test days in an open field.

Table 2.1. Neurobiological measures in higher success (HS) and lower success (LS) groups.



Measure	HS	LS	t	p
Brain weight (g)	1.792	1.813	-0.900	0.639
Cortical thickness (mm)	2.925	2.778	1.570	0.139
Pyramidal tract size (inch^2)	0.433	0.432	0.038	0.970
AchE density (inch^2)	110.839	110.294	0.062	0.927
Number of cells (mm^2)	392000	375000	1.480	0.085

Note. *df* = 14.

point scores nearly three times higher than the least successful rat. Large individual differences were not related to training and were not ameliorated by “rehabilitation”. Performance on skilled reaching did not correlate with measures of locomotor activity, nor were there obvious brain differences between high and low performing rats as measured by inspection of the brains, brain weight, measures of motor cortex thickness, cell numbers, pyramidal tract size, or AChE density. There were also no differences in the way that elements of the reaching movement were performed by high performing vs. low performing rats. Nevertheless, there was a relation between numbers of gestures associated with a reach and reaching success. Because gestures intrude into the act of limb transport, they may also impede accuracy. This result suggests that individual differences in skilled reaching are importantly influenced by the learning style of the subjects with animals prone to use stimulus-response (S-R) habits versus response orientation (R-O) strategies more likely to acquire disruptive reaching behavior.

The present experiment presents three lines of behavioral evidence to support the idea that the individual differences displayed by the rats on skilled reaching are meaningful. First, the rats were tested on a standard task in which reliable measures of performance could be obtained on each trial. It is also a task that has been widely used and one in which individual differences is readily observable (Metz, Jadavji, & Smith, 2005; Whishaw, 2000). The design of the experiment was also one in which the rats were tested repeatedly and it was confirmed that individual differences occurred on each iteration of the task both within days and across days and were consistent across the individual trials in a testing session. Second, a number of different measures of performance confirmed that the differences displayed by individual rats were reliable.

Measures of overall success, single reach success, and number of attempts were highly correlated. These measures have been used to define learning in skilled reaching (Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993) and to identify brain correlates of learning (Anderson, Eckburg, & Relucio, 2002; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Rosenzweig & Bennett, 1996; Withers & Greenough, 1989). Third, neither subjecting the rats to “rehabilitation” on a simpler tray reaching task nor overtraining had a significant effect on the relative performance of the rats.

There are a number of potential explanations of the individual differences documented in the present study, including differences in training, differences in more motor skill, or gross neural abnormalities. Each of these possibilities was examined in the design of the experiments. First, the possibility that the observed individual differences were simply due to training was examined in a number of ways. The initial training of the animals was extensive and all animals were trained until their performance reached asymptote. The animals were also given training on a different, simpler, tray-reaching task that has previously proved useful in the “rehabilitation” of brain-injured animals (Vergara-Aragon, Gonzalez, & Whishaw, 2003). Rehabilitation and subsequent over training did result in slight group improvement, but it did not change the distribution of individual differences. It is noteworthy that individual differences were not as apparent in the tray-reaching task, but this may be explained by the fact that the task is simple and produces quite uniform group performance. It is also noteworthy that some rats even reached for food with a different forelimb in the two tasks, consistent with previous reports that the limb preference of individual rats is not consistent across different forelimb-related tasks (Miklyaeva, Ioffe, & Kulikov, 1991). Thus, taken together, the procedures used in the present study appear to insure that individual differences are not due to inadequate training.

Second, there are several reports that animals can display developmental abnormalities such as cortical warts (Sherman, Galaburda, & Geschwind, 1985; Threlkeld et al., 2007), abnormal cortical development (Goodman & Gilbert, 2007; Schwartzkroin, Roper, & Wenzel, 2004), or have suffered stroke, tumors, or other brain injury (unpublished observations). Thus, there was concern that at least some of poor performing rats may have been suffering from preexisting nervous system abnormalities. Both the behavior measures and the anatomical measures argue against these possibilities. An examination of the movements used by the rats in skilled reaching using a movement element analysis based on EWMN showed that all of the rats used normal movements. Were differences in performance related to preexisting brain abnormalities, it would be expected that they would display abnormalities in the rotational movement of the limb and in use of the digits as these measures have proved sensitive to many kinds of brain injury including injury to the motor cortex (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Erickson, Gharbawie, & Whishaw, 2007), basal ganglia (Gharbawie, Auer, & Whishaw, 2006; Whishaw, Zeeb, Erickson, & McDonald, 2007), red nucleus (Whishaw & Gorny, 1996; Whishaw, Gorny, & Sarna, 1998) and spinal cord (McKenna & Whishaw,1999). The anatomical measures were also consistent with the conclusion that the observed individual differences were not related to gross brain abnormalities. In general, measures that have been found to be sensitive to brain injury (Jones, Chu, Grande, & Gregory, 1999; Kleim & Jones, 2008; Kolb, 2003; Schallert, Kozlowski, Humm, & Cocke, 1997) including of brain weight, cortical thickness, pyramidal tract size, motor cortex cell number, and AChE density revealed no obvious differences between rats and no differences that correlated with the behavioral measures. In future work other neurochemical differences in the motor system could be investigated and related to individual differences (Kleim, Chan, Pringle, Schallert, Procaccio, Jimenez, Cramer, 2006).

One behavioral difference that was related to individual differences in skilled reaching success was the measure of gestures. A gesture is a nonweight bearing movement that appears to have the characteristic of a fundamental movement primitive (Foroud & Whishaw, 2006). Based on the gesture analysis of reaching movement using LMA, a normal reaching movement consists of four gestures including advance of the limb toward the food, grasp by flexing and closing the digits, hand withdrawal toward the mouth, and release of the limb to its starting position. Each of these gestures is separated by a slight pause and changes in the movement direction and speed (Alaverdashvili, Foroud, Lim, & Whishaw, 2008).

These gestures are similar to the movement primitives identified by relatively long duration electrical stimulation of the motor cortex (Graziano, 2006; Ramanathan, Conner, & Tuszynski, 2006) and to elements in the development of reaching (von Hofsten & Rönnqvist, 1988; Wallace & Whishaw, 2003). Typically in a successful reach, each of these gestures is performed once in a complete reach sequence (advance-grasp-withdrawal-release). Sometimes the sequence is aborted at the transition points between gestures and this may result in the repetition of a gesture. For instance, on an unsuccessful trial, a rat might repeat the advance gesture to bring its hand to the vicinity of the food and/or grasp gestures if the hand did not contact the food. The failure in the accuracy of a reaching movement does not seem to be due to the abnormality or absence of any gestures. Results from the analysis of movement elements using EWMN indicated that the reaching elements and thus the gestures were normal. The rats with highest success scores made few unnecessary gestures while rats with poorer scores made many more gestures on each reach. For the present study, analysis of behavior began once preliminary training was complete. In future work it would be interesting to analyze behavior during pretraining. Such an analysis might reveal why and how some rats achieved an efficient reaching strategy whilst other rats developed excessive gestures.

Excessive gestures may be related to poor performance in two ways. They may signify that a rat has developed an inefficient strategy for obtaining food in that it has a poor approach, a poor posture, or a poor estimate of the location of the food and consequently is inaccurate in its reach. Gestures may also interfere with success directly. For example, a rat that makes repetitive grasping movements at the location of a food pellet increases its chance of knocking the food off the shelf and so encountering a failure on that trial. As an example, the intrusion of excessive gestures into the act of skilled reaching may be analogous to the intrusion of excessive syllables in speech to so causing stuttering (Mulligan, Anderson, Jones, Williams, & Donaldson, 2003; Prasse & Kikano, 2008). Thus, each movement, although in and of itself quite normal, nevertheless impairs execution and success.

One explanation for the development of excessive gestures by some of the rats is that they have developed as stimulus-response (S-R) approach to the task that makes them prone to develop motor habits inconsistent with optimal performance. Rats that are successful reachers may rely on a goal strategy, e.g., direct the hand to an appropriate spatial location. It is illustrative that Dickinson (1985) has described an example of performance decline following extensive training in which animals display a decreased response to a conditioned cue in favor of greater reliance on motor habit. According to this explanation, for some rats training with occasional successes serves to encourage them to engage in repetitive gestures rather than using a goal-directed movement.

This suggestion is consistent with other reports that there are individual differences in the strategies selected by rats in behavioral testing situations. Some animals are described as sign-trackers (they respond to a stimulus that signals reward) whereas others are described as goal-trackers (they respond to the location at which they get a reward (Boakes, 1977; Robinson & Flagel, 2009). Such differential tendencies may bias rats into those that favor a correct reach directed to the spatial location of the food vs. those that make repetitive movements until one is successful. It is interesting that an increase in gesture number also follows injury to the motor cortex by stroke in both rats (Alaverdashvili, Foroud, Lim, & Whishaw, 2008) and humans (Cirstea & Levin, 2000). Perhaps rats with motor cortex injury are less able to use a goal-oriented strategy and thus become more dependent upon a habit strategy.

There are features of the skilled reaching task that could serve to encourage a habit strategy on the part of rats. Rats do not monitor their reach visually as do primates (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008) but must learn to detect and localize the food using olfaction (Whishaw & Tomie, 1989). As they reach, they must remove their nose away from its pre reach orientation and so must learn to use a preprogrammed reach trajectory. It is possible that some rats hit on a goal strategy of taking care to directing their reaches to the food pellet location whereas other rats learn a habit strategy.

Although a habit strategy may increase missing the food, repeated movements could nevertheless result in sufficient reinforcement to achieve and maintain a habit response. Thus, depending upon the strategy that is selected, some rats become good performers in that they are successful with most reaches whereas others rely on gesture repetition, which makes them more prone to making errors.

In summary, rats display vast individual differences in skilled movement success in reaching for food. The differences are not easily explained by training procedures, general propensity to be active, or gross brain differences. It is suggested that individual differences in skilled reaching could derive from a particular strategy learned to obtain the food; with a goal oriented strategy likely to result in an accurate successful reach and a response oriented strategy resulting in repetitive movements that are less often successful. The strategy that is adopted by the latter rats is likely similar to a strategy of "learned baduse" described for rats that are impaired in skilled reaching due to motor cortex stroke (Alaverdashvili, Foroud, Lim, & Whishaw, 2008).

CHAPTER 3

Individual differences in skilled reaching for food emerges with practice

Abstract

The motor aspect of skilled reaching is similar in rodents and primates, but success in reaching by rodents is distinctively variable. Although, the individual differences in skilled reaching have been described after the skill acquisition in previous study, the emergence of the variability during initial training period has not been examined. Long-Evans rats were video taped as they learned to reach for single food pellets from a shelf. Frame by frame video analysis of the development of skilled reaching showed that the stages of the acquisition of the skill were similar in all animals. Individual differences in skilled reaching performance emerged after three days of training, well before the acquisition of the task was completed. The development of individual differences in skilled reaching during initial acquisition of the task are discussed in relation to the role of extensive practice in goal and habit learning of skilled reaching.

Introduction

Learning a new motor skill is associated with an effortful control of the behavior at the beginning of the acquisition and then with training becomes more automatic (James, 1890). Therefore to learn a new task such as skilled reaching for food, the demands are different during initial and later learning. After it is well practiced, the task is performed with relatively less effort. Characteristically, a performance is improved most rapidly across the first few sessions of training, with less improvement as performance approaches a plateau (Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Schmidt & Lee, 2005).

Skilled forelimb reaching for food in rodents (Whishaw & Pellis, 1990) is widely used as a model for neurobiological studies of motor function (Whishaw, Alaverdashvili, & Kolb, 2008; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993), motor skill learning (Greenough, Larson, & Withers, 1985; Kleim, Barbay, & Nudo, 1998; Remple, Bruneau, VandenBerg, Goertzen, & Kleim, 2001), and recovery from brain injuries (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Gharbawie & Whishaw, 2006; Whishaw & Gorny, 1996). Although the motor act of reaching in rats is similar with respect to movement elements, there is a distinctive variability once the task is learned. In chapter 2, the variability in skilled reaching performance of the adult rats was unchanged by overtraining and was related to the number of gestures (Gholamrezaei & Whishaw, 2009). The purpose of the present study was to examine and describe the details of individual differences between reaching performance of the rats during the acquisition period of the task.

In the present study, rats were trained on a single pellet-reaching task and their improvement in skilled reaching performance was analyzed and compared within and between training sessions. In order to compare motor task acquisition between two groups of rats with good and poor reaching skills, reaching behaviors in all training sessions were video recorded for subsequent frame-by-frame study.

Method

Subjects

Twenty-one male Long-Evans hooded rats, 120 days old and weighing 420-550 g at the beginning of the experiment from the University of Lethbridge vivarium were used. They were housed as pairs in standard Plexiglas cages (36 cm long, 20 cm wide, and 21 cm deep) with sawdust bedding in an animal colony room with a 12h light-dark cycle (lights on 7:30-19:30h) with temperature maintained at 22 °C. The experiment was conducted in compliance with the guidelines of the University of Lethbridge animal care committee and the Canadian Council for Animal Care, which complies with international standards for animal care.

Feeding

Prior to initial training, the rats were gradually food deprived to 90-95% of their normal body weight. Each rat received 20g of Purina rat chow once a day to maintain at that body weight. The rats also received 0.9g of 45mg dustless precision banana-flavored pellets (product #F0021, Bioserve Inc., Frenchtown, NJ, USA) for 3 days prior to initial training on the single pellet-reaching task to familiarize them with the taste and smell of the food. During training and the experiment, the banana-flavored pellets were served as targets in the reaching task. Each rat could receive up to 20 pellets per day depend on the animal's reaching accuracy.

Single pellet reaching apparatus

The single pellet-reaching box was made of transparent Plexiglas with 45 cm length, 14 cm width, and 35 cm height (Whishaw & Pellis, 1990). In the middle of the front wall, a 1 cm wide slit was extended from bottom of the box to a height of 15 cm. A 2 cm wide by 4 cm long shelf was attached to the outside of the front wall, 3 cm above the bottom of the box in front of the opening. There were two small indentations with 1.5 cm distance from the front wall aligned with each side of the slot to hold the food pellets. A food pellet in each indentation was accessible to the contralateral hand, because it pronates medially to grasp.

Single pellet reach training

Each animal was handled for 5 min on 5 consecutive days prior to the training and also each received twenty food pellets for 3 days before training began. Reach training was conducted in a different room from that used to house the animals. Training sessions took place every day at the same time. Rats were trained in the single pellet-reaching task for 18 days. All sessions were video recorded for the behavioral analysis. Training consisted of several steps, including the following:

(1) *Apparatus habituation*. Naïve animals were placed in the reaching apparatus individually for 10 min sessions daily. The objective was to introduce the rat to the reaching box with pellets on the shelf and to have the rat retrieve the pellet by hand or tongue. Once a rat was successfully retrieving the pellets, by moving the food pellets further away on the shelf, it was encouraged to use a hand to retrieve the food.

(2) *Establishing hand dominance.* To determine the dominant hand, initially pellets were presented in both indentations. Once a rat showed a clear preference for one hand, by making more reaching attempts with it, the food pellets were presented in the indentation contralateral to the dominant forelimb for three minutes of continuous reaching.

(3) *Full sequence reaching*. Full sequence reach training started after three minutes of continuous reaching. To obtain discrete reaching trials, a rat's behavior was shaped to leave the slot, walk to the rear wall of the box, turn, and approach the slot again for the next pellet. Thus, a rat was required to reposition its body for each reach. In addition, by withholding food on semi-randomly selected trials, rats were taught to sniff the shelf for a pellet and to reach only if a pellet was present (Alaverdashvili, Foroud, Lim, & Whishaw, 2008). Rats were trained in full sequence reaching for 14 days in which each training session consisted of 10 minutes or 20 trials.

Video recording

Skilled reach training sessions were video recorded for behavioral analysis. Video records were made with a Sony 3CCD camcorder with a shutter speed of 1000th of a second. Illumination for high shutter speed filming was provided by a cold light source (Whishaw & Pellis, 1990). Frame by frame analysis was done at 30 frames per second using a Sony digital videocassette recorder DSR-II.

Behavioral analysis

The behavioral analyses were made for all training sessions as following:

Early training

First training session began when a rat was placed in the reaching box and ended after 10 min with removing the rat out of the box. During initial training, rats learned how to orient the food pellet, advance their forelimb through the slot and grasp the food, and withdraw their hand to release the food pellet into their mouth. At the beginning of training, rats spent some time for familiarization to the box and the situation, which was used as the measures under time category. These measures were as follows:

1. Time spent before consuming food pellets at the start of the training

The rats spent different amounts of time exploring when first introduced to the reaching box. The amount of time spent before consuming food pellets was used for the first measure of the performance.

2. Time spent before making the first reach attempt

Time spent before first reach attempt was calculated.

3. Time spent before first successful reach

This measure calculated by adding the amounts of time spent from the beginning of the first training session until a rat made its first successful reach.

Continuous reaching and full sequence training

Reaching performance was analyzed for the endpoint measures such as the number of attempts and success percentage (Whishaw, 2005; Whishaw, Dringenberg, & Pellis, 1992). The reaching performances during continuous reaching and the full sequence training were investigated as follows:

Attempt. A reach attempt is defined as a forward movement of rat's preferred forelimb through the slot to grasp and obtain the food. Two forms of attempt can be made during a reach performance. One is a form of reaching attempt that includes aiming movement, which usually starts with digits flexed inside of the box. Another form is the reaching attempt that does not include aiming movement, which might be named as tapping attempts. This form of attempt usually starts with digits extend outside of the reaching box. A reach attempt could be successful or not. During training sessions, rats learned how to reach for a food pellet through trial and error. For example, rats made errors by reaching in the absence of a food pellet on the shelf (when a food pellet had been knocked off the shelf by inaccurate attempts). Attempts were counted as follows for all training sessions and calculated per trial:

1. Number of new aimed attempts

The reaching attempts with new aiming movement usually started with digits flexed inside of the box and advance of the limb through the slot toward the food pellet. This form of attempt could be successful or unsuccessful.

2. Number of tapping attempts

The tapping attempts were defined as repeating attempts for grasping a food pellet following an advance of the limb through the slot outside of the box, which had led to an unsuccessful grasp.

3. Number of attempts toward a food pellet

The number of attempts was counted when the food pellet was on the shelf.

4. Number of attempt errors

Attempt errors were the reaching attempts in the absence of the food pellet on the shelf. Attempt errors mostly happened during initial days of training, and sometimes after the food pellets had been knocked off the shelf by inaccurate attempts.

5. Total number of attempts

Total number of attempts was the overall number of attempts performed during reaching.

Successful reaches. Reaches that resulted in grasping the food pellet and obtaining the food pellet by releasing it into the mouth were defined as successful reaches. Successful reaches were recorded for each trial and session as the following:

1. First reach success

A reach attempt in which the food pellet was successfully grasped with the first advances of the limb and was consumed by the rat. First reach success percent was calculated by the following formula:

First reach success (%) = (Number of first reach successes/ Number of trials) × 100

2. Success with new aimed attempts

The successful reaches resulted from two or more new aimed attempts per trial were counted and the percentage were calculated by the following formula:

Successful reaches with new aimed attempts (%) = (Number of Successful reaches with new aimed attempts / Number of trials) × 100

3. Successful reaches made with tapping attempts

The successful reaches resulted from tapping attempts originated from the same aiming movement were counted and the percentage was calculated by the following formula:

Successful reaches with tapping attempts (%) = (Number of Successful reaches with tapping attempts / Number of trials) × 100

4. Total success

All reaches made by the rat that resulted in grasping the food pellet with the hand and obtaining the food pellet by releasing it into the mouth, despite the number of reach attempts, is defined as total success. Total success percent was calculated by the following formula:

Total success (%) = (Number of successes/ Number of trials) × 100

Other measures. Some other measures were made during full sequence training including number of missed trials, trial time, and time spent for making a trip.

1. Number of missed trials

When an animal returned to the front of the box for the next trial but did not reach for a food pellet was considered as a missed trial. The percentage of missed trials was calculated by the following formula:

Missed trials (%) = (Number of missed trials/ Number of trials) × 100

2. Trial time

On each trial the rat had to approach the slot from the back of the box, reach for the food pellet through the slot, and after attempting to gain the food, return to the rear of the box. Once a rat was trained, a trial was typically associated with the rat grasping the food or else knocked it off the shelf. Trial time for each training session was measured by dividing the total amount of time spent in a session by the number of the trials completed in that training session.

3. Trip time (time spent for going back of the box and returning to the front)

After completion of a trial, rats had to make a trip by going to the rear of the box and returning back to the front for the next trial. The time spent by each rat for completing a trip were measured for first 5 trials of each training session and then averaged.

Statistical analysis

The animals were divided into two groups according to their single reach success scores during last five days of training. Animals above the median of this rank order were assigned to the good reacher (GR) subgroup, whereas the animals below the median were assigned to the poor reacher (PR) subgroup. The behavioral data obtained from single pellet reaching task over training days were compared between GR and PR groups using repeated measures analysis of variance (ANOVA). Comparisons of means between groups for single days were performed using unpaired two-tailed *t* tests. Also learning plateaus are presented using ANOVA for repeated measures. To test correlations between behavioral variables, Pearson's correlation coefficient was applied. In all statistical analyses, a *p*-value of less than or equal to 0.05 was considered significant. All results were presented as mean ± the standard error of the mean (SEM).

Results

Body weight

Although the PR group had a higher body weight prior the skilled reach training, both groups lost weight similarly during training days and there were no differences in overall weight loss between the groups. The body weight of the groups prior to the food deprivation was significantly different between the GR and PR animals ($t_{19} = -2.707$, $p = 0.014$). Animals in both groups significantly lost weight during food deprivation days ($F_{3,57} = 89.217$, $p < 0.001$), with no group difference ($F_{1,19} = 0.156$, $p > 0.05$), and no interaction of day by group ($F_{4,76} = 0.421$, $p > 0.05$). Additional testing of single days for weight loss also showed no differences.

Early training

Three different time measures in the reaching box obtained from both groups included time spent before consuming food pellets, time spent before first reach, and time spent before first successful reach. The results showed that none of the measures did differ between the groups (Figure 3.1). The times spent before consuming food pellets ($t_{19} = 0.468$, $p > 0.05$), before first reach ($t_{19} = 1.244$, $p > 0.05$), and before first success ($t_{19} = 0.340$, $p > 0.05$) were not significantly different between the groups.

Continuous reach training

Continuous reach training consisted of 3 minutes of training for reaching toward food pellets, starting immediately after hand dominance was determined. The first and the last minutes of continuous reaching were scored in each group for end point measures. Results were as follows:

Attempts

Number of attempts toward a food pellet

The results indicated no differences between groups ($F_{1,19} = 0.579$, $p > 0.05$) during the first and last minutes of continuous reach practice. Also, there was no practice effect ($F_{1,19} = 1.685$, $p > 0.05$), or an interaction effect group by number of attempts in the first and last min ($F_{2,38} = 3.103$, $p = 0.094$). The statistical analysis indicated a group difference ($t_{19} = - 2.079$, $p = 0.058$) in the last minute of practice. The GR group exhibited

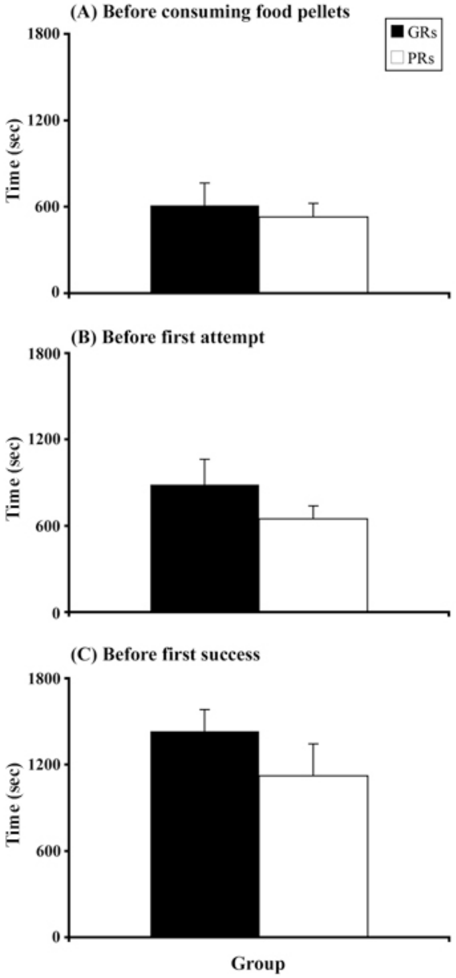


Figure 3.1. Early training time spent by GR and PR groups (mean ± *SEM*). (A) time spent before consuming a food pellet, (B) time spent before first reach, and (C) time spent before first success.

a decreased the number of reaching attempts during the last minutes of the continuous reaching whereas the PR group showed an increase of this type of attempt (Figure 3.2.A).

Number of attempt errors

The decreased number of attempts on an empty shelf was not significant between the first and last minutes of practice ($F_{1,19} = 3.583$, $p = 0.074$). Also, there was no overall difference between the groups ($F_{1,19} = 0.862$, $p > 0.05$), or an interaction effect ($F_{2,38} = 0.005$, $p > 0.05$) (Figure 3.2.A).

Number of new aimed attempts

The number of new aimed attempts during first and last minutes of continuous reaching were compared between groups and no difference was found ($F_{1,19} = 0.024$, $p > 0.05$). This type of attempts also was not significantly different between the first and last minutes of reaching ($F_{1,19} = 1.294$, $p > 0.05$), and there was no interaction effect ($F_{2,38} = 0.182$, $p > 0.05$) (Figure 3.2.B).

Number of tapping attempts

Although there was no significant difference between the number of tapping attempts during the first and last minute of continuous reaching ($F_{1,19} = 0.624$, $p > 0.05$) or between groups ($F_{1,19} = 1.888$, $p > 0.05$), an interaction effect of group by number of tapping attempts in the first and last min was found ($F_{2,38} = 4.129$, $p = 0.056$). Rats in PR group exhibited an increased use of tapping attempts during the last minute of continuous reaching (Figure 3.2.B). Statistical analysis of the last minute of continuous reach practice showed a group difference in the number of tapping attempts ($t_{19} = - 2.746$, $p = 0.013$).

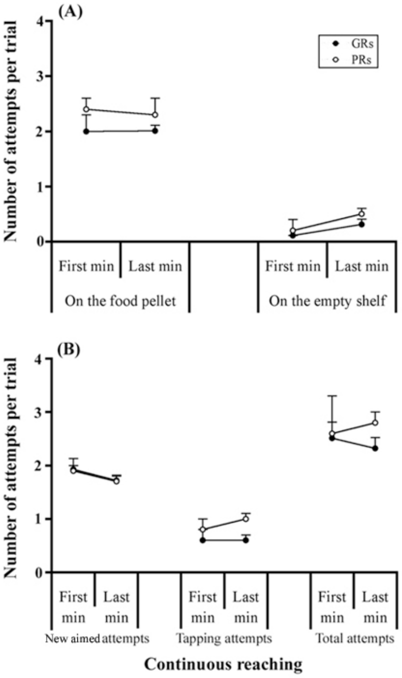


Figure 3.2. Number of attempts per trial during first and last minutes of continuous reaching of GR and PR groups (mean ± *SEM*). (A) number of attempts toward a food pellet and toward an empty shelf, and (B) number of new aimed, tapping and total attempts.

Total attempts

Overall, there was no significant difference between groups in the number of total attempts ($F_{1,19} = 0.871$, $p > 0.05$) or in the first and last minutes of practice ($F_{1,19} = 0.028$, $p > 0.05$). Also, there was no interaction effect of group by number of attempts in the first and last min of practice ($F_{2,38} = 0.767$, $p > 0.05$) (Figure 3.2.B).

Success

Success made with new aimed attempts (%)

Successful attempts made with new aiming movement significantly increased with more practice from the first minute to the last minute of continuous reaching in both groups ($F_{1,19} = 9.704$, $p = 0.006$). This type of success significantly differ between the groups ($F_{1,19} = 4.496$, $p = 0.047$), the GR group showed an increased percentage of success compared to the PR group. No interaction effect of group by minutes of practice was found ($F_{2,38} = 1.816$, $p > 0.05$) (Figure 3.3.A).

Success made with tapping attempts (%)

Overall, no significant difference was found in the success percentage with tapping attempts between the groups ($F_{1,19} = 0.008$, $p >0.05$). There was no significant effect of success in the first and last minutes of practice ($F_{1,19} = 0.351$, $p > 0.05$), or an interaction effect of group by success in the first and last minutes of practice ($F_{2,38} = 0.009$, $p > 0.05$) (Figure 3.3.A).

Single reach success (%)

Single reach percent success was measured in both groups during the first and last

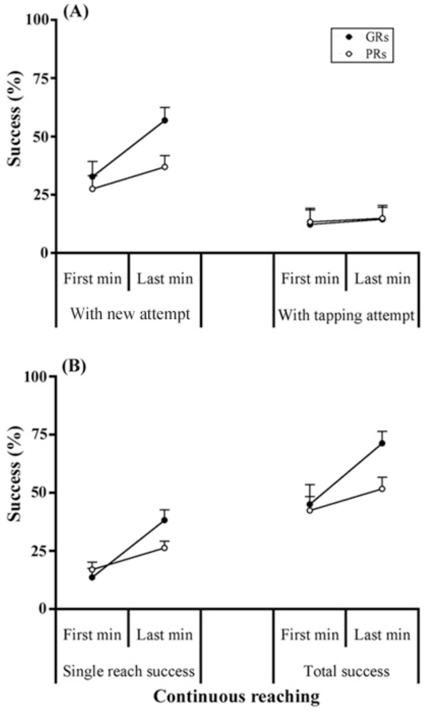


Figure 3.3. Success percentage during first and last minutes of continuous reaching of GR and PR groups (mean ± *SEM*). (A) success (%) with new aimed and tapping attempts, and (B) single reach success and total success.

minutes of continuous reaching and the results showed a significant effect of practice ($F_{1,19}$ = 23.607, $p < 0.001$). Although there was not a significant difference between groups ($F_{1,19}$ = 1.183, $p > 0.05$), an interaction of groups by minutes of practice ($F_{2,38}$ = 4.799, $p = 0.041$) was found. An increase in the single reach success was more apparent in the GR group (Figure 3.3.B). Testing of the last minute of continuous reach practice showed a group difference in which rats in GR group were significantly improved in the single reach success (t_{19} = 2.229, $p < 0.05$).

Total success (%)

The results indicated that total success percentage significantly increased with the amount of practice in both groups ($F_{1,19}$ =12.404, $p = 0.002$). But it did not differ between the groups ($F_{1,19}$ = 2.359, $p > 0.05$) and no interaction effect was found ($F_{2,38}$ = 2.780, $p > 0.05$) (Figure 3.3.B). Testing of the last minute of practice indicated the group difference in the total success with the more improvement in the GR group (t_{19} = 2.724, $p < 0.05$).

Full sequence reach training

Full sequence reach training started after three minutes of continuous reaching. The training consisted of shaping the rats' behavior to leave the slot, going to the back of the box, and returning to the front of the box for the next reach. Rats were trained in the full sequence reaching for 14 days and their reaching performance was analyzed for numbers of attempts, success percentage and other variables such as number of missed trials, trial time, and trip time.

Attempts

Number of new aimed attempts

The number of new aimed attempts per trial declined during training sessions

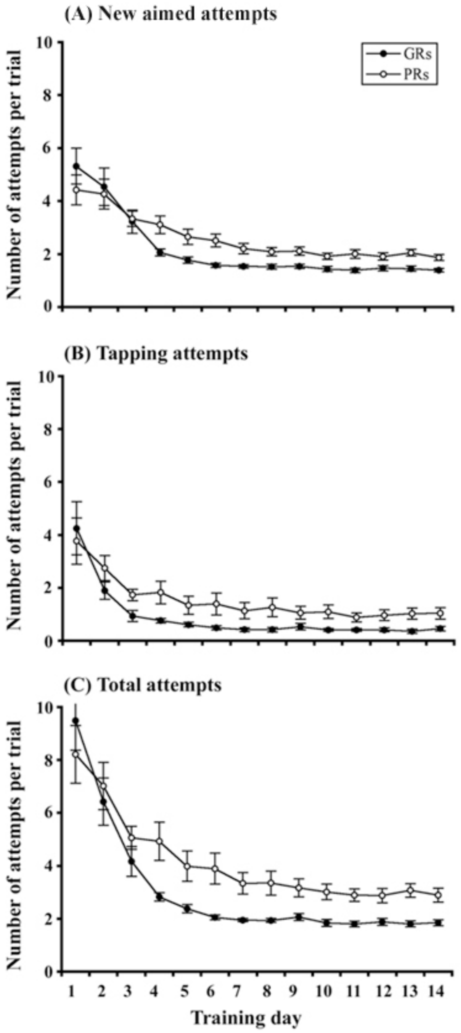


Figure 3.4. Number of attempts per trial during 14 days of full sequence training between GR and PR groups (mean ± *SEM*). (A) number of new aimed attempts, (B) number of tapping attempts, and (C) number of total attempts.

($F_{13,247} = 31.878$, $p < 0.001$), and it decreased more in the GR rats ($F_{1,19} = 4.900$, $p < 0.05$). Also the difference in learning effect was significant. An interaction effect of groups by training days was significant ($F_{13,247} = 1.834$, $p < 0.05$). The number of new aimed attempts plateaued at day 7 in both groups ($F_{7,133} = 1.924$, $p > 0.05$) (Figure 3.4.A). Testing of single days showed that the GR rats had a lower number of new aimed attempts than the PR rats from the fourth day of training on ($t_{19} = -2.760$, $p = 0.012$) and thereafter (p values < 0.01).

Number of tapping attempts

The number of tapping attempts per trial decreased over training sessions ($F_{13,247} = 20.470$, $p < 0.001$), and this decline was greater in the GR rats ($F_{1,19} = 4.771$, $p < 0.05$). No interaction effect of groups by training days was found ($F_{13,247} = 0.789$, $p > 0.05$). The number of tapping attempts plateaued on day 6 of training in both groups ($F_{8,152} = 1.341$, $p > 0.05$) (Figure 3.4.B). Testing of single days revealed less number of tapping attempts in the GR relative to the PR rats from the third day of training ($t_{19} = -2.628$, $p = 0.017$) and thereafter (p values < 0.05).

Number of total attempts

The number of total attempts per trial decreased over training days ($F_{13,247} = 44.104$, $p < 0.001$). The animals in the GR group showed a greater decrease in the number of total attempts ($F_{1,19} = 6.649$, $p = 0.018$). An interaction effect of groups by training days was found ($F_{13,247} = 1.794$, $p < 0.05$) (Figure 3.4.C). The number of total attempts plateaued from day 7 in both groups ($F_{7,133} = 1.883$, $p > 0.05$). Testing of single days revealed that the GR animals showed fewer total attempts on fourth day of the training ($t_{19} = -2.740$, $p = 0.013$) and thereafter (p values < 0.01).

Number of attempts toward a food pellet

The number of attempts per trial when reward was on the shelf decreased over training sessions ($F_{13,247} = 1.766$, $p < 0.05$), and there was a significant group difference ($F_{1,19} = 14.823$, $p = 0.001$). An interaction effect of groups by training days was found ($F_{13,247} = 2.075$, $p < 0.05$). The numbers of attempts plateaued on day 7 of the training period in both groups ($F_{7,133} = 1.636$, $p > 0.05$) (Figure 3.5. A). Testing of single days yielded lower number of tapping attempts in the GR rats on fourth day of the training ($t_{19} = -3.502$, $p = 0.002$) and thereafter (p values < 0.01).

Number of attempt errors

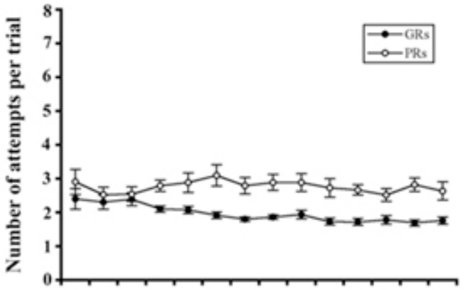
The number of attempts per trial toward on an empty shelf decreased over training sessions in both groups ($F_{13,247} = 42.118$, $p < 0.001$). The groups did not differ ($F_{1,19} = 1.121$, $p > 0.05$) and no interaction effect of groups by training days was found ($F_{13,247} = 1.632$, $p > 0.05$) (Figure 3.5. B). Testing single days showed the groups were different in making attempts on an empty shelf during days 4-7 (p values < 0.05) with the GR rats making less attempts on the empty shelf. No difference was found between groups (p values > 0.05) during first three days and last week of the training.

Success

Success with new aimed attempts (%)

Successful attempts made with new aiming did not differ over training days ($F_{13,247} = 1.274$, $p > 0.05$). Success significantly differ between the groups ($F_{1,19} = 18.842$, $p < 0.001$), the GR group showed a higher success score than the PR group. No interaction effect of groups by training days was found ($F_{13,247} = 1.384$, $p > 0.05$) (Figure 3.6.A).

(A) Attempts toward a food pellet



(B) Attempts on an empty shelf

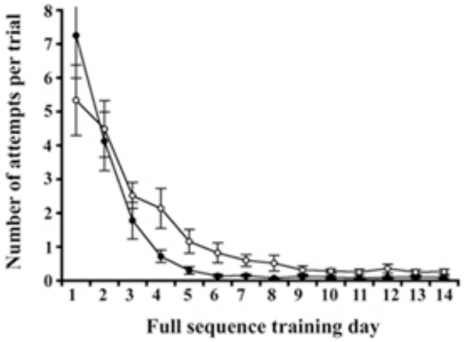


Figure 3.5. Number of attempts per trial during 14 days of full sequence training between GR and PR groups (mean ± *SEM*). (A) number of attempts toward a food pellet, and (B) number of attempts toward an empty shelf.

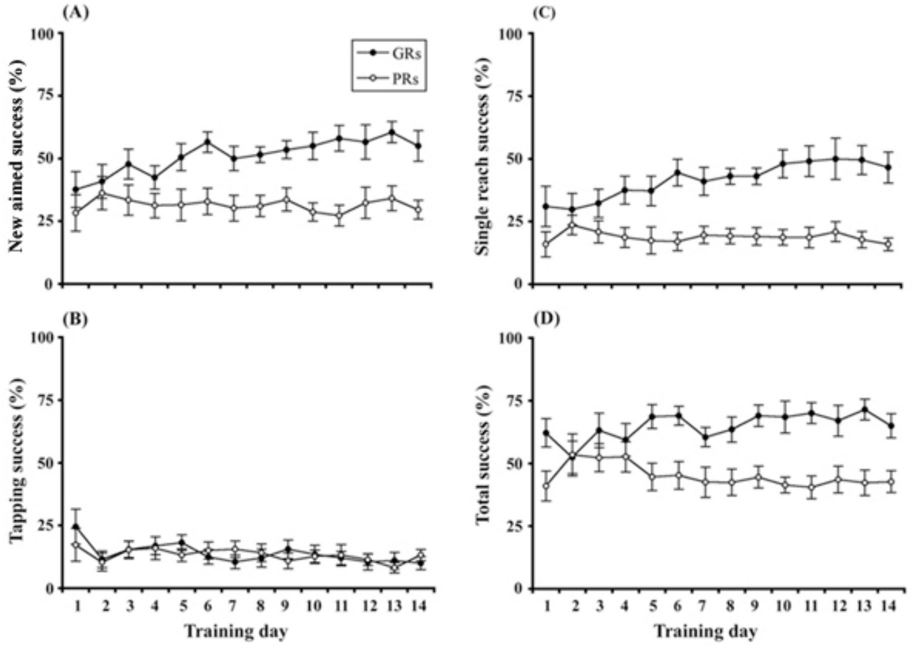


Figure 3.6. Success percentage during 14 days of full sequence training between GR and PR groups (mean ± *SEM*). (A) success with new aimed attempts, (B) success with tapping attempts, (C) single reach success, and (D) total success.

Testing of single days showed that the GR rats had a higher success (%) than the PRs, starting from the fifth day of the training ($t_{19} = 2.266$, $p = 0.035$) and thereafter (p values < 0.01).

Success with tapping attempts (%)

The only measure that did not differ with more practice throughout training days was success on tapping attempts. Repeated measures ANOVA revealed that success with tapping attempts (%) did not differ over training days ($F_{13,247} = 1.505$, $p > 0.05$) and also successful reaching on tapping attempts was not different between groups ($F_{1,19} = 0.049$, $p > 0.05$). In addition, no interaction effect of groups by training days was found ($F_{13,247} = 0.548$, $p > 0.05$) (Figure 3.6.B).

Single reach success (%)

Single reach success percentage did not differ over training days ($F_{13,247} = 1.256$, $p > 0.05$) but the GR and PR groups were different significantly in making successful single reaches ($F_{1,19} = 36.160$, $p < 0.001$). A marginal interaction effect of groups by training days was found ($F_{13,247} = 1.681$, $p = 0.065$) (Figure 3.6.C). Testing of single days showed that the GR rats had a higher single reach success percentage than the PRs on the fourth day of training ($t_{19} = 2.799$, $p = 0.011$) and thereafter (p values < 0.05).

Total success (%)

Total success percentage did not differ over training days ($F_{13,247} = 0.414$, $p > 0.05$) but the GR and PR groups were different significantly ($F_{1,19} = 20.402$, $p < 0.001$). An interaction effect of groups by training days was found ($F_{13,247} = 1.845$, $p < 0.05$) (Figure 3.6.D). Testing of single days showed that the GR rats had a higher total success

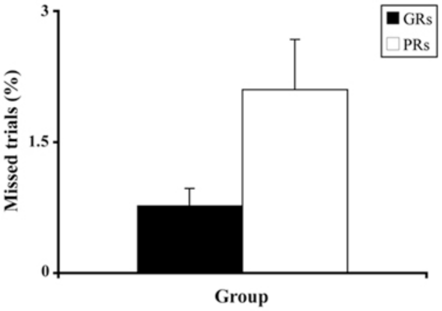


Figure 3.7. Missed trials (%) in GR and PR groups (mean ± *SEM*).

(%) than the PR rats on the first day ($t_{19} = 2.561$, $p = 0.019$), fifth day ($t_{19} = 3.308$, $p = 0.004$) of the training and thereafter (p values < 0.01).

Missed trials (%)

Missed trials (%) decreased significantly over training days ($F_{13,247} = 6.400$, $p < 0.001$). The result revealed that the PR group showed a higher missed trials (%) than the GR group ($F_{1,19} = 4.398$, $p < 0.05$) (Figure 3.7). Also, an interaction effect of groups by training days was found ($F_{13,247} = 2.534$, $p = 0.003$).

Trial time

Trial time decreased significantly over training days ($F_{13,247} = 63.001$, $p < 0.001$) but it did not differ between groups ($F_{1,19} = 2.834$, $p > 0.05$) and no interaction effect of groups by training days was found ($F_{13,247} = 1.128$, $p > 0.05$) (Figure 3.8.A).

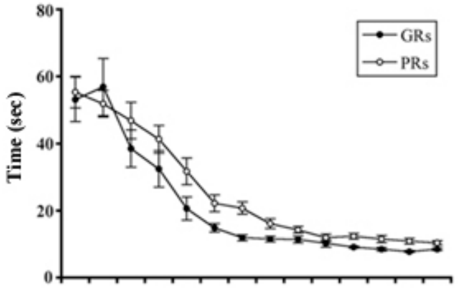
Trip time

Trip time decreased significantly over training days ($F_{13,247} = 86.198$, $p < 0.001$). The groups were not different in time spent to make a trip ($F_{1,19} = 3.177$, $p > 0.05$). No interaction effect of groups by training days was found ($F_{13,247} = 1.453$, $p > 0.05$) (Figure 3.8.B).

Discussion

The objective of the present study was to investigate individual differences in skilled reaching performance and its emergence during initial learning in the adult naïve rats. One group of rats with higher success scores and lower number of attempts was designated as GRs and the other group was designated as PRs. Both groups of rats learned the task as confirmed by several factors including, increase in successful reaches, decrease in the number of attempts, decrease in the number of errors, and decrease in the

(A) Trial time



(B) Trip time

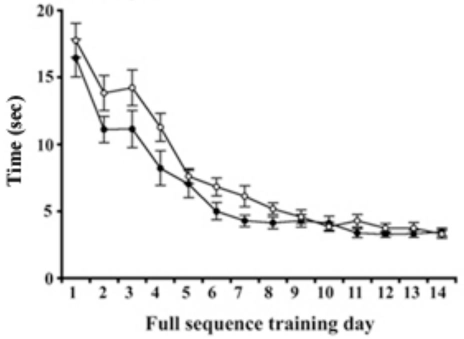


Figure 3.8. Spent time for making a trial and a trip during 14 days of full sequence training between GR and PR groups (mean ± *SEM*). (A) trial time, and (B) trip time.

time spent for a trial or a trip. The findings are discussed in relation to the idea that rats with extensive training develop different strategies in learning a novel task, which leads to two different reaching abilities.

The present results are in line with a previous study (Gharbawie & Whishaw, 2006) showing that the act of reaching was formed and completed in both groups with similar serial and temporal organization. Comparison of learning between the GR and PR animals indicated that the skilled reaching performance was similar between groups at the beginning of the training, but individual differences started to emerge with practice. The difference in skilled reaching performance between groups was observable on the fourth day of the training and thereafter. It was also found that the animals in the PR group were different than the animals in the GR group in the number of missed trials throughout the training sessions. The considerable and consistent individual differences found in skilled reaching of the subjects in the present study support the idea that the individual differences in skilled reaching are reliable and meaningful.

The single pellet-reaching task has been chosen for a detailed study of the difference in reaching performance of the rats because it is a task that has been widely used in many different studies (Gholamrezaei & Whishaw, 2009; Metz, Jadavji, & Smith, 2005; Whishaw, 2000). Rats display large variation in skilled reaching performance after completion the training period (Gholamrezaei & Whishaw, 2009). The single pellet-reaching task also provides reliable measures of performance such as single reach success, total success, and number of attempts. These measures have been used previously to define learning in skilled reaching (Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993). In the present study, some other measures related to time spent, missed trials, and different types of attempts in addition to previous ones were used to provide a more detailed investigation of the phenomenon.

Earlier studies have shown that skilled reaching in rats consists of three components, orientating toward a food pellet to locate it by sniffing, transporting the hand to the food pellet during which the digits are shaped to the target to grasp it, and withdrawal of the limb for releasing the food into the mouth (Gharbawie & Whishaw, 2006). Results of the present study indicated that although there was variation in the time taken by individual rats to progress from one component to the next, the order and the amount of time spent to learn these three components of reaching was similar in both groups. That is, the amount of time spent before consuming the food pellets, before first reaching attempt, and before first successful reach was equivalent in rats that became GR and PR. In addition, the skilled reaching performances in both groups plateaued similarly on the seventh day of training. Despite of the skill improvement differences, both groups took the same amount of time to learn the skill and to reach the asymptotic level of their group. Therefore, it can be concluded that the act of reaching was formed in both groups with similar serial and temporal organization.

The results of the present study indicate that the difference in the groups' performance started to emerge after task learning was established and as performance improved with practice. For example, during the first phase of the training, which was 3 minutes of reaching toward a food pellet without going to the back of the box, both groups made a similar number of attempts and success at the first minute of practice but their reaching attempts started to diverge after a couple of minutes practicing the same movements. The PR group began to make more tapping attempts whereas the GR group started to perform fewer tapping attempts, which could be considered as a sign of the skill improvement.

Although both groups improved in successful reaches, the GR group's improvement was considerably higher than the PR group's improvement. This differentiation in learning also was observable after the introduction of the second phase of training, which involved forming discrete reaching trials involving going to the back of the box and returning to the front for the next reaching act. Similarly, after introducing the second phase of training to the animals, the difference between groups became clearer. The PR group made more reaching attempts on each trial and the GR group began to improve success by making fewer attempts thus achieving a higher level of success. The learning difference between the groups was observable during initial days of practice and was completed on fourth day of the training. Although, both groups learned to make more accurate reaching attempts with more practice but the reaching skill improved in the GR group through increase of the success level and decline of the unnecessary reaching attempts, which was not observed in the PR group performance. The level of success of the PR group did not change through the full sequence training and the decline of the unnecessary reaching attempts was not as pronounced as it was in the GR group.

There are a number of potential explanations of the divergence of the reaching performance by the groups. According to the study described in Chapter 1, the group difference was marked with lower success and higher number of attempts in the poor reachers that was not related to: (1) inadequate training (2) gross neural abnormalities (3) difference in other motor skills (4) abnormalities of the reaching movement elements

(Gholamrezaei & Whishaw, 2009). The present study also found that the amount of weight loss could not be a factor for the difference in skilled reaching displayed by rats, because results revealed that the overall weight loss was similar between groups.

There are two potential explanations for the development of individual differences found in the present study. One relates to the higher number of missed trials in the PR group. There is evidence that rats do not locate the food visually as do primates (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008), and use olfaction to detect and localize the food (Whishaw & Tomie, 1989). Therefore, it is possible that the PR group show a higher number of missed trials because of impairment in olfactory detection. This impairment might be the origin of a poor estimate of the location of the food.

The second possibility could be related to the higher number of missed trials displayed by the PR group. The PR rats may have developed a habit strategy through extensive practice of making the same sequence of movements over and over, irrespective of outcome. Recent studies have suggested that the reward-related actions such as skilled reaching behavior depend on two different learning processes. One of which is involved in the relationship between the action and their consequences that governs goal-directed behavior and the other is involved in the formation of stimulus-response associations that are thought to control habitual actions (Balleine & O'Doherty, 2010; Dickinson, 1994; Dickinson, Balleine, Watt, Gonzalez, & Boakes, 1995). Therefore, the learning strategy that the PR group might have developed was one of stimulus-response associations. Although training conditions were similar for both groups, the PR rats may have developed a motor habit (performing the full sequence of movements consists of going to the back of the box, returning to the front and making reach attempts) as a sensorimotor response that is more reflexive in nature. On the other hand, the GR rats might have used goal-directed strategy and controlled their reaching performance in relation to the consequences and thus optimized their performance through directing their hand to the appropriate spatial location of the target.

Different learning strategies acquired by rats have been reported in other reward-related actions such as conditioned approach behavior in which animals developed tendencies to approach different stimuli in similar testing situations. One group responded to the stimulus or cue that signaled reward delivery whereas other group preferentially approached and responded to the location where the reward was delivered (Boakes, 1977; Flagel, Akil, & Robinson, 2008; Robinson & Flagel, 2009). The differential learning strategies may bias some rats to make successful reaches directed to the spatial location of the reward whereas other rats making more attempts toward the food just because they learned this response may lead to the reward by occasional prior successful reaches. Therefore, depending on the strategy, some animals become the good reachers with accurate reaching skills marked by higher success level and lower number of attempts while others became poor reachers.

In conclusion, the objective of the present study was to investigate individual differences in skilled reaching performance and its emergence by analyzing behavior of two groups of animals that were defined by good and poor reaching skills. The study provides support for the reliability of the individual differences found in skilled reaching for food in female rats vs. male rats. The study also demonstrates that the difference in reaching success and the number of attempts between groups started to emerge with more practice of the same sequence of movements, as early as first couple of minutes after initial training. It is suggested that the differences in skilled reaching could derive from two potential possibilities. First, it might be related to the impairment in olfactory processes in the PR group. Second, it could derive from the particular learning strategy adopted by each group of animals. A goal-directed strategy adopted by the GR group, in which reaching performance is controlled in relation to the consequences and is associated with the reward by locating the target accurately and directing forelimb to the appropriate spatial location of the food. On the other hand, a response-oriented strategy adopted by the PR group, in which reaching movement is performed as a sensorimotor response that is more habitual and reflexive in nature without less associative link to the reward, results in repetitive movements and a lower level of success. The study thus suggests that the differences in the skilled reaching might be influenced by the learning style of the rats.

CHAPTER 4

Behavioral sensitization induced by repeated administration of amphetamine or nicotine has no effect on subsequent acquisition and performance of skilled reaching behavior but has differential effects on animals with good or poor reaching skills

Abstract

Repeated administration of psychostimulant drugs can cause persistent alterations in the brain and behavior including long lasting structural plasticity, the development of enduring locomotor sensitization, and alterations in reward-related learning and memory. The purpose of this investigation was two fold: (1) to determine whether behavioral sensitization induced by prior repeated administration of amphetamine or nicotine has beneficial effects on the acquisition and performance of the skilled reaching behavior and (2) to investigate their possible effects on the individual differences in skilled reaching performance. Two separate experiments with similar experimental design were conducted to produce behavioral sensitization in rats using amphetamine and nicotine. After producing behavioral sensitization, rats were trained in single pellet reaching task and their reaching behavior was recorded, analyzed, and compared. Results indicated that behavioral sensitization prior to skilled reach training was not beneficial to learning the task or to subsequent performance of the sensitized rats. Comparing the animals with good and poor reaching skills in sensitized and non-sensitized groups showed that amphetamine sensitization had a different effect on subgroups that displayed good or poor reaching skills. There was an increase in successful reaches made by the sensitized-good reachers relative to the good reachers in non-sensitized group. But no differences were found in the endpoint measures of the sensitized-poor reachers compared with non-sensitized-poor reachers. Sensitization to nicotine had a detrimental effect on the way movements were made. The results are discussed with respect to the deferential effects of psychostimulant drugs on individual differences in skilled reaching behavior.

Introduction

Repeated administration of drugs of abuse such as amphetamine and nicotine can cause persistent alterations in the brain and behavior. For example it can lead to long-lasting structural plasticity in the nucleus accumbens and prefrontal cortex (Brown & Kolb, 2001; Robinson & Kolb, 1997, 2004; Singer et al., 2009), development of locomotor sensitization (Bevins & Palmatier, 2003; Dougherty & Ellinwood, 1981; Robinson & Becker, 1986; Vezina, McGehee, and Green, 2007), alterations in reward-related learning and memory (Childress et al., 1993; Hyman & Malenka, 2001; Rogers et al., 1999), and enhancement of drug-related behaviors such as drug-seeking and -taking (Pierce & Kalivas, 1997; Robinson & Becker, 1986; Robinson & Berridge, 1993; Tiffany & Carter, 1998; Vanderschuren & Everitt, 2005). Repeated exposures to addictive drugs can also cause long-term increases in behaviors toward natural rewards such as food (Harmer & Phillips, 1998; Klein, Gehrke, Green, Zentall, & Bardo, 2007; Wyvell & Berridge, 2000, 2001), and sex (Fiorino & Phillips, 1999; Nocjar & Panksepp, 2002). The long-lasting changes in behavior and psychological functions are probably mediated by neurochemical drug effects (Robinson & Becker, 1986; Robinson, Mocsary, Camp, & Whishaw, 1994) on structural modifications in patterns of synaptic connectivity in relevant neural circuits (Greenough, 1984; Kolb & Teskey, 2010; Kolb, Forgie, Gibb, Gorny, & Rowntree, 1998; Robinson & Kolb, 1997), which were developed gradually and outlasted for months after termination of the drug treatment (Paulson, Camp, & Robinson, 1991).

There is a considerable debate regarding the efficacy of amphetamine or nicotine on learning a novel motor skill, enhancing motor performance, and facilitating forelimb motor recovery after motor cortex stroke (Alaverdashvili, Lim, & Whishaw, 2007; Gladstone et al., 2006; Gonzalez, Gharbawie, & Kolb, 2006; Lim, Alaverdashvili, & Whishaw, 2009; Papadopoulos et al., 2009). Variable behavioral effects have been reported in response to prior or concurrent repeated administration of amphetamine or nicotine. For example, some studies have shown that amphetamine and nicotine improve skilled reaching for food in both rats and primates (Adkins & Jones, 2005; Barbay et al., 2006; Gilmour et al., 2005; Gonzalez, Gharbawie, Whishaw, & Kolb, 2005; Ramic et al., 2006). However, some other studies have found negative results (Alaverdashvili, Lim, & Whishaw, 2007; Lim, Alaverdashvili, & Whishaw, 2009; Platz et al., 2005). Although the difference in the dose of drug and the timing schedule of drug administration may contribute to the variations reported, it is interesting that drug-induced behavioral changes and neurochemical adaptations may vary considerably between individual subjects as well (Cain, Coolon, & Gill, 2009; Deminiere, Piazza, Le Moal, & Simon, 1989; Gingras & Cools, 1997; Scholl, Feng, Watt, Renner, & Forster, 2009). Rats exhibit individual differences in the development of behavioral sensitization (Perkins et al., 2009; Scholl, Feng, Watt, Renner, & Forster, 2009), the attribution of incentive salience to reward-related cues (Robinson & Flagel, 2008), and the development of approach behavior (Flagel, Clinton, Watson, Robinson, & Akil, 2007; Simon, Mendez, & Setlow, 2009; Taylor & Jentsch, 2001).

Because of the long lasting effect of behavioral sensitization induced by administration of stimulant drugs on the patterns of synaptic connectivity and its effects on the acquisition of a novel task, it was hypothesized that behavioral sensitization induced by prior repeated exposure to amphetamine or nicotine affect the acquisition of skilled reaching behavior and the effects would be different among animals' skilled reaching behavior. Nelson and Killcross (2006) have shown that amphetamine sensitization disrupts the acquisition of goal-directed actions and accelerates the progression of habitual responding. Thus, the current experiments examined whether sensitization induced by amphetamine or nicotine accelerates the dominance of habitual responding of rats as a feature of poor reaching skills.

Two separate experiments with similar experimental design were conducted to produce behavioral sensitization in rats using amphetamine and nicotine. After producing behavioral sensitization, rats were trained in single pellet reaching task and their reaching behavior were recorded, analyzed, and compared on several measures. First, the acquisition of skilled reaching was compared between drug-treated and saline-treated animals. Second, because of the considerable debate regarding the efficacy of amphetamine and nicotine to improve forelimb motor skill, the reaching performances of the drug-treated animals were compared with those of the saline-treated rats. Third, because the drugs of abuse might potentially have different effects on the performances of animals with good or poor reaching skills, each group (drug-treated and saline-treated) were divided into two subgroups, good reacher (GR) and poor reacher (PR) based on their reaching performance. Comparisons were made on the end-point measures of total success, single reach success, and the number of attempts per trial. Also, in order to investigate potential drug effects on movement elements used for reaching (Whishaw & Pellis, 1990), the performance were analyzed using a rating scale derived from Eshkol-Wachmann Movement Notation (EWMN) analysis of reaching (Eshkol & Wachmann, 1958; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993). In addition, reaching movements were analyzed and compared for the non-kinematic features of the movement (gestures) derived from Laban Movement analysis Notations of reaching (LMA; Laban, 1971).

Method

Subjects

The subjects were 23 female Long-Evans rats, 3 months old and weighing 200-300 g at the beginning of each experiment. Female Long-Evans were used because of the greater rates of sensitization than males (Robinson, 1984; Robinson & Becker, 1986). The animals were housed in standard Plexiglas cages in an animal colony room with food and water available and a 12h light-dark cycle (lights on 7:30-19:30h). The room temperature maintained at 22° C. The experiments were in compliance with the guideline of the University of Lethbridge animal care committee and the Canadian Council for Animal Care, which complies with international standards for animal care. Each experiment consisted of two groups: an experimental group, including amphetamine or nicotine (N=13) and a saline group (N=10).

Drug administration

The intermittent schedule of psychostimulant drug administration was used to induce behavioral sensitization in rats using amphetamine and nicotine in two separate experiments. Rats were acclimatized for a week in the animal care facilities before the animals receive daily injections. In line with previous research (Kolb et al., 2003; Domino, 2000), animal received intraperitoneal (i.p.) injections of either *d*-amphetamine sulfate or 0.9% saline in the first experiment and either nicotine hydrogen tartrate salt or 0.9% saline in the second experiment for 11 consecutive days.

On the first and last test day, animals in the amphetamine group were received 0.5 mg/kg amphetamine (weight of the salt) and animals in the nicotine group were received 0.2 mg/kg nicotine; for the 9 days in between the amphetamine group were given 1mg/kg amphetamine and the nicotine group were given 0.4 mg/kg nicotine.

Horizontal locomotor activity

Horizontal locomotor activity (HLA) was measured in identical wired hanging cages 35 cm length, 26 cm width, and 20 cm height. Each cage was equipped with two pairs of infrared emitter-detector photocells that were positioned along the long axis 1 cm above the floor and 8 cm from the front and back of the cage. Photocell interruptions served as a measure of HLA. Data are presented as total horizontal locomotor activity during 30 min prior to and 90 min following drug/saline administration. All rats were habituated to the locomotor activity boxes for two days before any drug treatment commence. After two days of habituation, rats were placed in the activity boxes and their HLA were recorded 30 min before and 90 min following drug/saline administration for 11 consecutive days.

Food restriction

The day after last injection in each experiment, the animals were food deprived to 90-95% of their normal body weight. Each rat received 18g of Puria rat chaw once a day to maintain at that body weight. Also they received 0.9g of 45 mg dustless precision banana-flavored pellets (product# F0021, Bioserve Inc., Frenchtown, NJ, USA) for 3 days prior to initial training on the single pellet-reaching task for familiarization with the taste and smell of the food pellets. During the training and testing sessions, the banana-flavored pellets were served only as targets in the reaching task. Each animal could receive up to 20 pellets per day depend on the reaching accuracy.

Single pellet reaching

The single pellet-reaching box was made of transparent Plexiglas with 45 cm length, 14 cm width, and 35 cm height. In the middle of the front wall, a 1 cm wide slit is extended from bottom of the box to a height of 15 cm. A 2 cm wide by 4 cm long shelf is attached to the outside of the front wall, 3 cm above the bottom of the box in front of the opening. There are two small indentations with 1.5 cm distance from the front wall aligned with each side of the slot to hold the food pellets. A food pellet in each indentation is accessible only to the contralateral forelimb, because the hand pronates medially to grasp (Whishaw & Pellis, 1990).

Reach training sessions were conducted at approximately the same time each day in a testing room. Rats were trained on the single pellet-reaching task for 14 days. On the first day of training, rats were placed individually in the reaching apparatus with pellets on the shelf for 10 minutes to have them retrieved the food pellet by hand or tongue. Once the pellets were retrieved successfully, the pellets were moved further away on the shelf to encourage the rat to use a hand and reach for the food. Pellets were initially presented in both indentations to determine the forelimb dominance. Once a rat showed a clear preference for one hand, by making more reaching attempts with it, a single food pellet was presented in the indentation contralateral to the preferred forelimb for three minutes of continuous reaching. In order to obtain discrete reaching trials, rats were required to reposition their body on each trial. They were shaped to leave the slot, walk to the rear wall of the box, turn and approach the slot again for the next pellet. In addition, by withholding food on semi-randomly selected trials, rats were taught to sniff the shelf for a pellet and to reach only if a pellet was present. Single pellet reaching tests (each session consisted of 20 trials) were performed for five consecutive days after the completion of the training sessions.

Video recording

Video records were made using a Sony 3CCD camcorder with a shutter speed of 1000th of a second. Illumination for high shutter speed filming was provided by a cold light source (Whishaw & Pellis, 1990). Frame by frame analysis was done at 30 frames per second using a Sony digital videocassette recorder DSR-II.

Behavioral analysis

The behavioral analyses were made for training sessions as following:

Early training

First training session began when a rat was placed in the reaching box and ended after 10 min with removing the rat out of the box. During initial training, rats learned how to orient the food pellet, advance their preferred forelimb through the slot and grasp the food, and withdraw their hand to release the food pellet into their mouth. At the beginning of training, rats spent some time for familiarization to the box and the acquisition of the task, which was used as the measures under time category. These measures were as follows:

1. Time spent before consuming food pellets at the start of the training

Rats spent different amounts of time exploring when were introduced to the reaching box. The amount of time spent before consuming a food pellet was used for the first measure of the performance.

2. Time spent before making the first reach attempt

Time spent before first reach attempt was calculated despite of the success or failure of the reach.

3. Time spent before first successful reach

This measure calculated by adding the amounts of time spent from the beginning of the first training session until a rat made its first successful reach.

Continuous reaching and full sequence training

Reaching performances during training and testing sessions were analyzed for the endpoint measures such as the number of attempts and success percentage (Whishaw, 2005; Whishaw, Pellis, & Gorny, 1992).

End point measures

A testing session consisted of twenty trials. On each trial, the rat had to approach the slot from the back of the box, reach for the food pellet through the slot, and after attempting to get the food (grasping the food or else knocked it off the shelf), return to the rear of the box. Reaching performances were analyzed in each trial for the number of attempts, first reach success and total success (Whishaw, 2005; Whishaw, Pellis, & Gorny, 1992).

Attempt. The number of reach attempts was counted in each trial. A reach attempt is defined as a forward movement of rat's preferred forelimb to the slot in the front wall of the reaching box in an attempt to grasp and obtain the food. A reach attempt could be successful or not depending on the accuracy of the reaching movement.

First reach success. First reach success is defined as a reach attempt in which the food pellet is grasped with the first advance of the forelimb and is consumed by the rat. First reach success scores were calculated as follows:

First reach success (%) = (Number of first reach successes/ Number of trials) × 100

Total success. Success is defined by reaches resulted in obtaining food by grasping the pellet with the hand despite the number of reach attempts. Total success percent was calculated as follows:

Total success (%) = (Number of successes/ Number of trials) × 100

Movement element analysis

Reaching movements were analyzed using a rating scale derived from Eshkol-Wachmann Movement Notation (EWMN) analysis of reaching (Eshkol & Wachmann, 1958; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993) based on the analysis of the relations and changes of relations between the body parts involved in the reaching movement. A reach was subdivided into ten reaching elements including; *(1) Digits to the midline:* The reaching limb is lifted from the floor so that the tips of the digits are aligned with the midline of the body. *(2) Digits closed:* As the limb is lifted, the digits are flexed and closed, the hand is supinated and the wrist is partially flexed. *(3) Aim:* The hand and elbow are carried inward to the midline of the body, with the hand located just under the mouth. *(4) Advance:* The limb is advanced directly through the slot toward the food pellet. *(5) Digits extend:* During the advance, the digits extend toward the food pellet. *(6) Arpeggio:* When the hand is over the food pellet, it pronates from digit 5 through to digit

2, and at the same time the digits open. *(7) Grasp:* The digits close and flex over the food pellet, with the hand remaining in place, and the wrist is slightly extended to lift the food. *(8) Supination I:* As the hand is withdrawn, it supinates by almost 90°. *(9) Supination II:* Once the hand is withdrawn from the slot to the mouth, it supinates further by about 45° to place the food pellet in the mouth. *(10) Release:* The mouth contacts the hand and the digits open to release the food pellet.

Ten reaching elements were analyzed and scored for first three successful reaches of the last test session. Each of the reaching elements was rated on a three-point scale. A score of "0" was given for a normal movement, a score of "0.5" for an abnormal movement, and a score of "1" for the absence of a movement (Piecharka, Kleim, & Whishaw, 2005; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993).

Gesture analysis

Reaching movements were analyzed using the "Expressive Reaching Scale" derived from Laban Movement analysis Notations of reaching (LMA), which provides a quantifying method for the non-kinematic features of the movement (Foroud & Whishaw, 2006). Based on this rating scale, a gesture is defined as one action made by one limb or one limb segment and a reach is subdivided into four gestures including, (1) advance: The limb is advanced toward the food pellet. *(2) Grasp:* The digits are closed over the food or near the food pellet. *(3) Withdraw:* The hand is withdrawn toward the mouth. *(4) Release:* The digits are flexed and the limb is moved away from the mouth.

Reaching performances on the last test session were analyzed and the number of gestures was calculated for the first five trials. A score of "1" was given for each gesture. Because a reach consisted of four gestures, a minimum of four score could be given to a successful reach. However, both successful and failed reaches could be associated with additional gestures (Alaverdashvili, Foroud, Lim, & Whishaw, 2008).

Statistical analysis

The results were subject to multivariate and repeated measures analysis of variance (ANOVA). Follow-up analyses of significant interactions were performed with Bonferroni post hoc tests. Also, comparisons of means between groups were performed using paired and unpaired *t*-tests. In all statistical analyses, a *p*-value of less than or equal to 0.05 was considered significant. All results were presented as mean $\pm$ the standard error of the mean (SEM).

Results

Horizontal locomotor activity

Psychomotor sensitization was obtained during 11 days of drug administration in both experiments. Due to temporary malfunction of the apparatus the data related to 2 rats in the amphetamine group and 1 rat in the saline group of the first study was not available and the analysis was conducted according to the data obtained from the rest of the animals. Although no significant difference in HLA was found between groups during 30 min habituation time before drug administration in both studies (AMPH vs. saline: $F_{1,18} = 2.018$, $p > 0.05$ [Figure 4.1.A]; NIC vs. saline: $F_{1,21} = 1.842$, $p > 0.05$ [Figure 4.1.C]), a higher HLA was observed in the drug groups during 90 min testing after injections (Figure 4.1). Repeated measures ANOVA showed a significant effect of group ($F_{1,18} = 337.401$, $p < 0.001$), along with an interaction of group by day

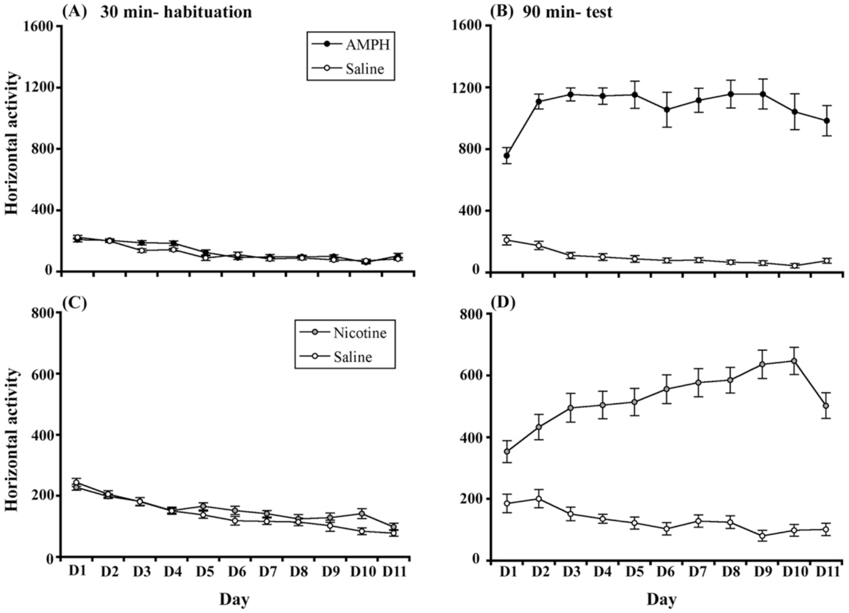


Figure 4.1. Horizontal activity before and after drug injections over 11 consecutive days (mean ± *SEM*). (A) 30-min habituation time before injection (AMPH vs. Saline), (B) 90-min test after injection (AMPH vs. Saline), (C) 30-min habituation time before injection (Nicotine vs. Saline), and (D) 90-min test after injection (Nicotine vs. Saline).

($F_{10,180} = 3.517$, $p < 0.001$) (Figure 4.1.B). Repeated measures ANOVA revealed a significant effect of nicotine vs. saline group ($F_{1,21} = 89.767$, $p < 0.001$), day ($F_{10,210} = 2.921$, $p = 0.002$), and an interaction of group by day ($F_{10,210} = 11.854$, $p < 0.001$) (Figure 4.1.D).

Psychomotor sensitization was confirmed also by comparing the effects of the half dose drug administration on the first and last day of the treatment in both groups. Paired *t*-test showed a significant increase of locomotor activity between the first and last day of drug administration in the AMPH group (t_{10}= -2.391, $p < 0.05$), and the NIC group (t_{12}= -2.817, $p < 0.05$).

Single pellet reaching

Three days after the last injections, animals in both experiments were trained in the single pellet reaching task for 14 days and tested for 5 more days. Performances were analyzed for initial learning, first and last minutes of continuous reaching, and full sequence training days (D1, D3, D5, D7, D9). Also all five testing sessions were scored and analyzed for endpoint measures, movement elements and number of gestures.

Early training

Three different time spent in the reaching box were measured in all groups in both experiments including, time spent before consuming a food pellet, time spent before first reach, and time spent before first successful reach. The results showed that none of the measures did differ between the drug-treated animals and the saline groups (Figure 4.2). The time spent before consuming food pellets [AMPH vs. saline: ($t_{21} = -0.729$, $p > 0.05$); NIC vs. saline: ($t_{21} = -0.939$, $p > 0.05$)], before first reach [AMPH vs. saline: ($t_{21} = -0.442$, $p > 0.05$); NIC vs. saline: ($t_{21} = 0.658$, $p > 0.05$)], and before first success [AMPH

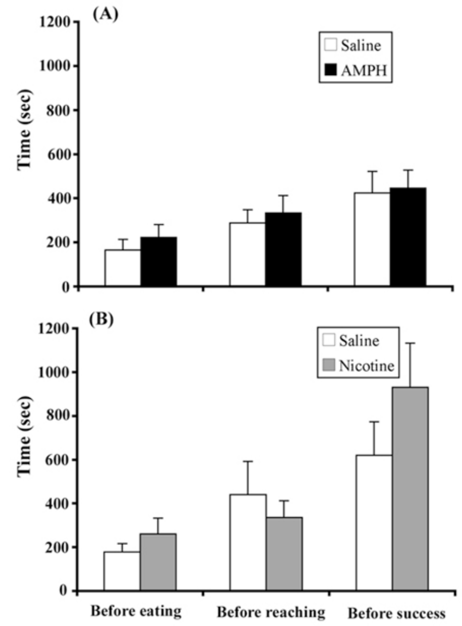


Figure 4.2. Early training time spent by the drug- and saline-treated animals (mean ± *SEM*). (A) AMPH vs. saline, and (B) Nicotine vs. saline.

vs. saline: (t_{21} = -0.172, $p > 0.05$); NIC vs. saline: (t_{21} = -1.162, $p > 0.05$)], were not significantly different between the groups.

First and last minutes of continuous reaching

Continuous reach training consisted of 3 minutes of training for reaching toward food pellets, starting immediately after hand dominance was determined. The first and the last minutes of continuous reaching were scored in each group for endpoint measures. A summary of results for endpoint measures is illustrated in Figure 4.3. The results indicated that saline animals had higher successful reaches compare to drug-treated animals during continuous reach training. The group difference was observed for total success in both experiments [AMPH vs. saline: ($F_{1,21}$ =5.246, $p < 0.05$); NIC vs. saline: ($F_{1,21}$ =5.315, $p < 0.05$)] and single reach success only in nicotine study ($F_{1,21}$ =7.403, $p < 0.05$). The main effect of practice was found for single reach success and number of attempts only in the AMPH vs. saline groups [single reach success: ($F_{1,21}$ =5.617, $p < 0.05$); number of attempts: ($F_{1,21}$ =6.096, $p < 0.05$)], but not in the nicotine vs. saline animals [single reach success: ($F_{1,21}$ = 0.310, $p > 0.05$); number of attempts: ($F_{1,21}$ = 0.172, $p > 0.05$)]. Also a group by minutes of practice interaction was found for total success in nicotine vs. saline group ($F_{1,21}$ =5.947, $p < 0.05$) but not in the AMPH study ($F_{1,21}$ = 0.176, $p > 0.05$).

Full sequence training

Full sequence reach training started after three minutes of continuous reaching. The training consisted of shaping the rats' behavior to leave the slot, going to the back of the box, and returning to the front of the box for the next reach. Rats were trained in full

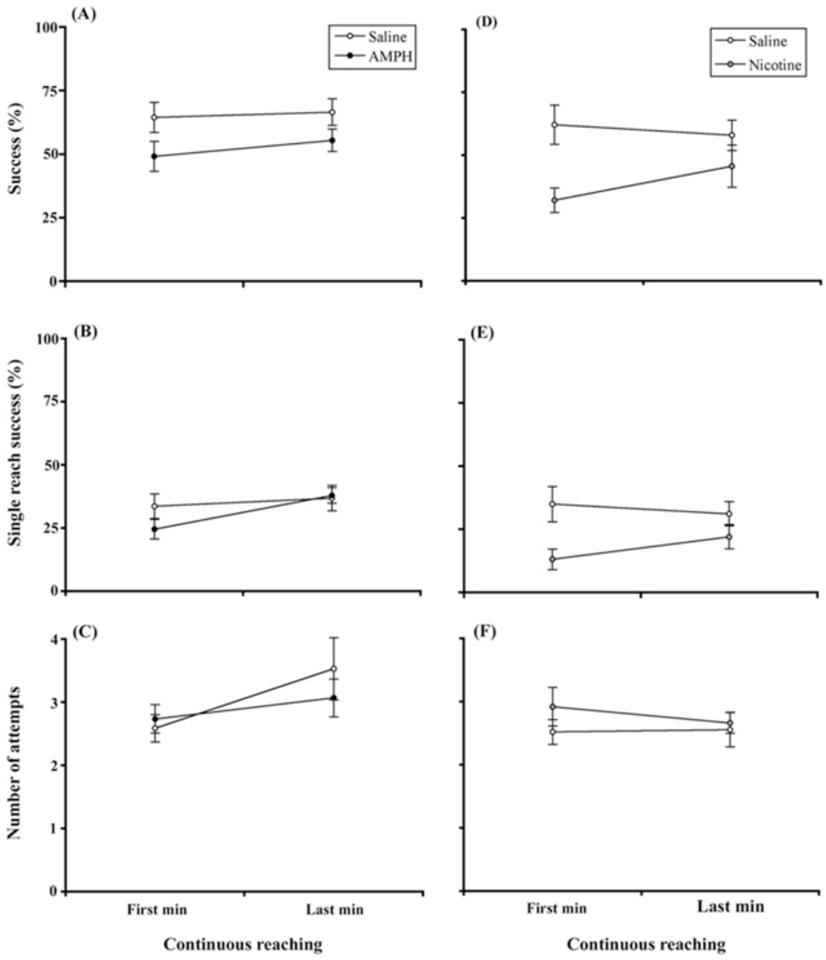


Figure 4.3. Endpoint scores during first and last minutes of continuous reaching in sensitized and non-sensitized animals (mean ± *SEM*). (A) total success (%), (B) single reach success (%), (C) number of attempts in AMPH vs. saline groups, and (D) total success (%), (E) single reach success (%), and (F) number of attempts in nicotine vs. saline groups.

sequence reaching and their reaching performance on 1st, 3rd, 5th, 7th, and 9th days of training were scored and analyzed for the endpoint measures during training period. A summary of endpoint measures during training days is illustrated in Figure 4.4. Repeated measure ANOVA revealed that the groups did not differ in total success [AMPH vs. saline: ($F_{1,21} = 0.107$, $p > 0.05$); NIC vs. saline: ($F_{1,21} = 0.116$, $p > 0.05$)], single reach success [AMPH vs. saline: ($F_{1,21} = 1.476$, $p > 0.05$); NIC vs. saline: ($F_{1,21} = 1.073$, $p > 0.05$)], and the number of attempts [AMPH vs. saline: ($F_{1,21} = 1.694$, $p > 0.05$); NIC vs. saline: ($F_{1,21} = 1.399$, $p > 0.05$)] during training days. The main effect of day found only for the number of attempts [AMPH vs. saline: ($F_{4,84} = 24.047$, $p < 0.001$); NIC vs. saline: ($F_{4,84} = 27.063$, $p < 0.001$)], and not for the total success [AMPH vs. saline: ($F_{4,84} = 0.588$, $p > 0.05$); NIC vs. saline: ($F_{4,84} = 0.937$, $p > 0.05$)] or single reach success [AMPH vs. saline: ($F_{4,84} = 2.037$, $p > 0.05$); NIC vs. saline: ($F_{4,84} = 2.160$, $p > 0.05$)]. No day by group interactions were found [AMPH vs. saline: ($F_{4,84} = 2.666$, $p > 0.05$); NIC vs. saline: ($F_{4,84} = 0.402$, $p > 0.05$)].

Single pellet reaching test sessions

After completion of training days rats in both experiments were tested for 5 consecutive days and their reaching performances were analyzed for endpoint measures. Results indicated that drug-treated rats in both studies did not differ in total success scores, single reach success scores, and the number of attempts relative to saline-treated rats (Figure 4.5).

AMPH vs. saline group: repeated measures ANOVA on the total success showed

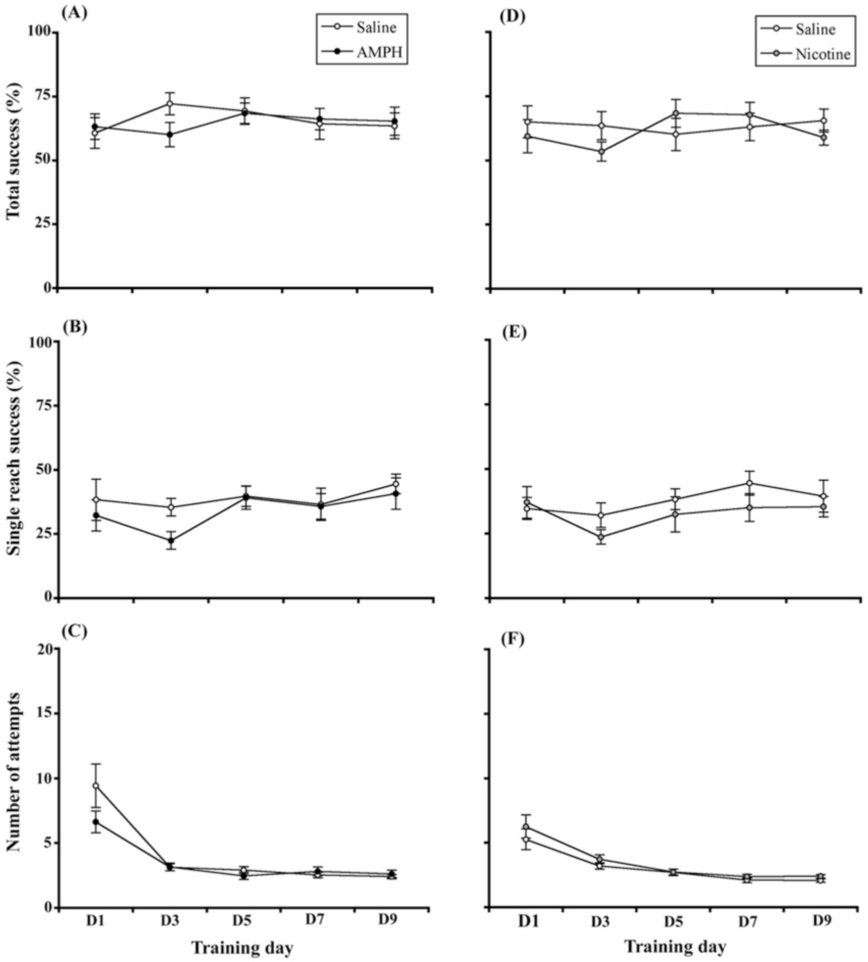


Figure 4.4. Endpoint scores during full sequence training in sensitized and non-sensitized animals (mean ± *SEM*). (A) total success (%), (B) single reach success (%), (C) number of attempts in AMPH vs. saline group, and (D) total success (%), (E) single reach success (%), and (F) number of attempts in nicotine vs. saline groups.

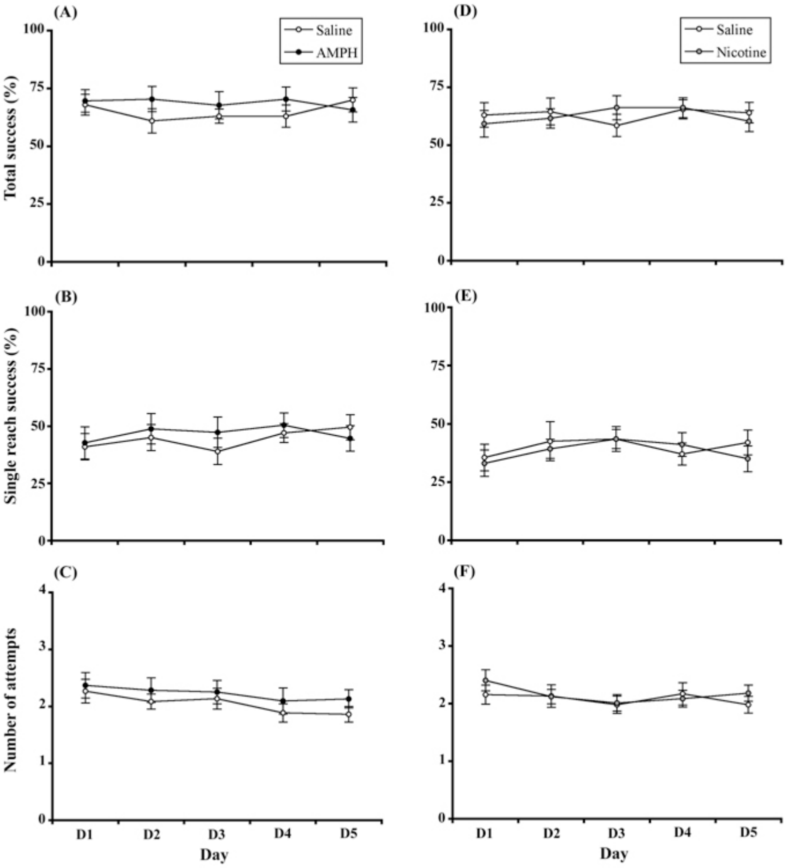


Figure 4.5. Endpoint scores during five test sessions between drug- and saline-treated groups (mean ± *SEM*). (A) total success (%), (B) single reach success (%), (C) number of attempts in AMPH vs. saline group, and (D) total success (%), (E) single reach success (%), and (F) number of attempts in nicotine vs. saline groups.

no significant difference between groups ($F_{1,21} = 0.319$, $p > 0.05$), with no effects of test day ($F_{4,84} = 0.701$, $p > 0.05$), but a marginal interaction of group by day was found ($F_{4,84} = 2.347$, $p = 0.061$) (Figure 4.5.A). Results for single reach success scores indicated no difference between groups ($F_{1,21} = 0.103$, $p > 0.05$), with no effects of test day ($F_{4,84} = 1.818$, $p > 0.05$) or interaction ($F_{4,84} = 1.242$, $p > 0.05$) (Figure 4.5.B). Repeated measures ANOVA on the number of attempts per trial revealed that although there was no difference in the number of attempts made per trial between groups ($F_{1,21} = 0.516$, $p > 0.05$), there was a significant effect of test days ($F_{4,84} = 4.315$, $p = 0.003$). Also no test day by group interaction was found ($F_{4,84} = 0.266$, $p > 0.05$) (Figure 4.5.C).

Nicotine vs. saline group: similar results were found in the second study, repeated measures ANOVA on the total success showed no significant difference between groups ($F_{1,21} = 0.005$, $p > 0.05$), with no effects of test day ($F_{4,84} = 0.726$, $p > 0.05$) or interaction ($F_{4,84} = 1.357$, $p > 0.05$) (Figure 4.5.D). Results from single reach success scores indicated no difference between groups ($F_{1,21} = 0.069$, $p > 0.05$), with no effect of test day ($F_{4,84} = 1.985$, $p > 0.05$) or interaction ($F_{4,84} = 0.739$, $p > 0.05$) (Figure 4.5.E). Repeated measures ANOVA on the number of attempts per trial revealed that although there was no difference in the number of attempts made per trial between groups ($F_{1,21} = 0.141$, $p > 0.05$), there was a significant effects of test day ($F_{4,84} = 3.694$, $p = 0.008$). Also no test day by group interaction was found ($F_{4,84} = 1.761$, $p > 0.05$) (Figure 4.5.F).

Individual differences (Good reachers vs. poor reachers)

The animals in each group were then divided into two subgroups: good reachers (GR) and poor reachers (PR) according to their single reach success scores over five test sessions (Gholamrezaei & Whishaw, 2009). Animals above the median of this rank order were assigned to the GR subgroup, whereas the animals below the median were assigned to the PR subgroup. The behavioral data obtained from single pellet reaching task over testing days and also behavioral sensitization data during 11 days of drug/saline administration were compared between GR and PR subgroups within drug vs. vehicle main category.

Single pellet reaching test sessions

Results showed a significant difference in total success scores between the AMPH-treated GRs vs. saline-injected GRs (t_9= -3.039, $p < 0.05$) in which GRs of the AMPH group showed higher reaching success relative to GRs of the saline group. Although AMPH-treated PRs showed lower success level than the saline-injected PRs, the difference was not found significant (t_{10}= 0.418, $p > 0.05$).

Two-way ANOVA showed a significant main effect of skill on all three endpoint measures including total success, single reach success, and number of attempts between subgroups of animals within both drug vs. saline groups, but no effect of group or skill by group interaction was found. The results of both experiments are summarized for each of the endpoint measures in the following.

Total success. Two-way ANOVA on total success (Figure 4.6.A & 4.6.D) showed a significant main effect of skill in both experiments [AMPH vs. saline: ($F_{1,19} = 24.902$, $p < 0.001$); NIC vs. saline: ($F_{1,19} = 8.562$, $p = 0.009$)], but no effect of group [AMPH vs. saline: ($F_{1,19} = 1.289$, $p > 0.05$); NIC vs. saline: ($F_{1,19} = 0.004$, $p > 0.05$)], or skill by group interaction [AMPH vs. saline: ($F_{1,19} = 3.395$, $p = 0.081$); NIC vs. saline: ($F_{1,19} = 0.706$, $p > 0.05$)].

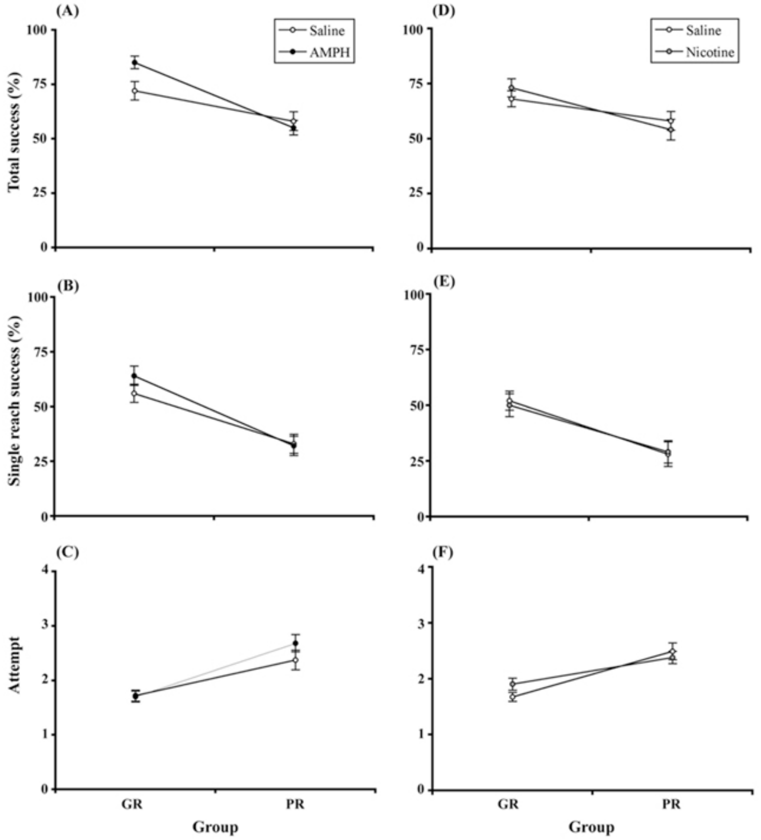


Figure 4.6. Endpoint measures during five test sessions between drug- and saline-treated rats with good vs. poor reaching skills (mean ± *SEM*). (A) total success (%), (B) single reach success (%), (C) number of attempts in AMPH vs. saline group, and (D) total success (%), (E) single reach success (%), and (F) number of attempts in nicotine vs. saline groups.

Single reach success. The similar results were found on single reach success (Figure 4.6.B & 4.6.E) in both experiments with a significant main effect of skill [AMPH vs. saline: ($F_{1,19} = 34.865$, $p < 0.001$); NIC vs. saline: ($F_{1,19} = 25.089$, $p < 0.001$)], with no effect of group [AMPH vs. saline: ($F_{1,19} = 0.634$, $p > 0.05$); NIC vs. saline: ($F_{1,19} = 0.04$, $p > 0.05$)], or skill by group interaction [AMPH vs. saline: ($F_{1,19} = 1.148$, $p > 0.05$); NIC vs. saline: ($F_{1,19} = 0.08$, $p > 0.05$)].

Number of attempts. Also similar results were found on the number of attempts (Figure 4.6.C & 4.6.F) with a significant main effect of skill [AMPH vs. saline: ($F_{1,19} = 22.677$, $p < 0.001$); NIC vs. saline: ($F_{1,19} = 17.633$, $p < 0.001$)], with no effect of group [AMPH vs. saline: ($F_{1,19} = 2.105$, $p > 0.05$); NIC vs. saline: ($F_{1,19} = 0.143$, $p > 0.05$)], or skill by group interaction [AMPH vs. saline: ($F_{1,19} = 2.609$, $p > 0.05$); NIC vs. saline: ($F_{1,19} = 1.219$, $p > 0.05$)].

Comparing data of the NIC-treated subgroups showed that nicotine diminished the difference between the GRs and PRs on the number of attempts. The NIC-treated GRs displayed an increase in the number of attempts ($F_{1,11} = 3.751$, $p > 0.05$).

Behavioral sensitization in GRs vs. PRs

Although there was a significant difference between behavioral sensitization demonstrated by drug-treated vs. saline-treated groups (AMPH vs. saline: $F_{3,16} = 100.877$, $p < 0.001$; NIC vs. saline: $F_{3,19} = 27.253$, $p < 0.001$), no significant difference was found between drug-treated GR vs. PR subgroups (AMPH-treated GRs vs. PRs: $F_{1,9} = 0.038$, $p > 0.05$; NIC-treated GRs vs. PRs: $F_{1,11} = 0.086$, $p > 0.05$).

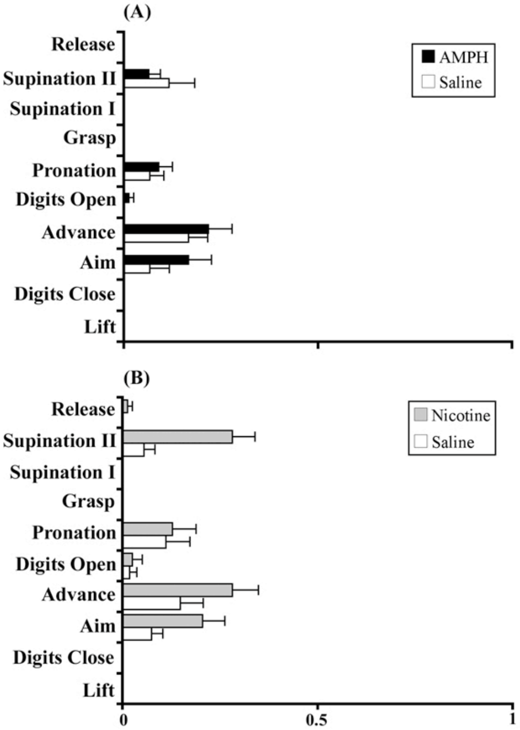


Figure 4.7. Movement elements of reaching on the last day of testing (mean ± *SEM*). (A) AMPH vs. saline group, and (B) Nicotine vs. saline group. *Note:* Nicotine-treated animals displayed impairments in the aim and supination II.

Movement elements

The ten movement components of three successful reaches for the last day (day 5) of the testing sessions were examined carefully frame by frame. The analysis showed that the movement elements made by animals that sensitized by AMPH were not significantly different than the saline group (Figure 4.7.A). Repeated measures ANOVA indicated a significant effect of element ($F_{9,189} = 9.801$, $p < 0.001$), with no effect of group ($F_{1,21} = 0.469$, $p > 0.05$) or a group by element interaction ($F_{9,189} = 0.842$, $p > 0.05$).

Repeated measures ANOVA on movement elements of NIC vs. saline groups revealed a significant effect of group ($F_{1,21} = 5.645$, $p < 0.05$), element ($F_{9,189} = 11.609$, $p < 0.001$), and a group by element interaction ($F_{9,189} = 3.113$, $p = 0.002$). Post hoc analysis ($p < 0.05$) showed that nicotine-treated rats were impaired significantly on aim, advance, and supinating the hand to present the food to the mouth (Figure 4.7.B). Nicotine-treated animals with incorrect aiming movements advanced their limb diagonally toward the food pellet and they had difficulty in supinating their hand completely to present food to the mouth.

In order to determine whether there was a treatment effect on the reaching elements of the subgroups with good and poor reaching skills, performances of the four subgroups were compared (Figure 4.8).

Repeated measures ANOVA on reaching elements between the AMPH vs. saline subgroups revealed that there was no effect of subgroups ($F_{3,19} = 0.171$, $p > 0.05$), but a significant effect of element ($F_{9,171} = 8.514$, $p < 0.001$). The element by subgroup interaction was not significant ($F_{27,171} = 0.692$, $p > 0.05$) (Figure 4.8.A). Comparison of the reaching elements between the nicotine vs. saline subgroups indicated no significant

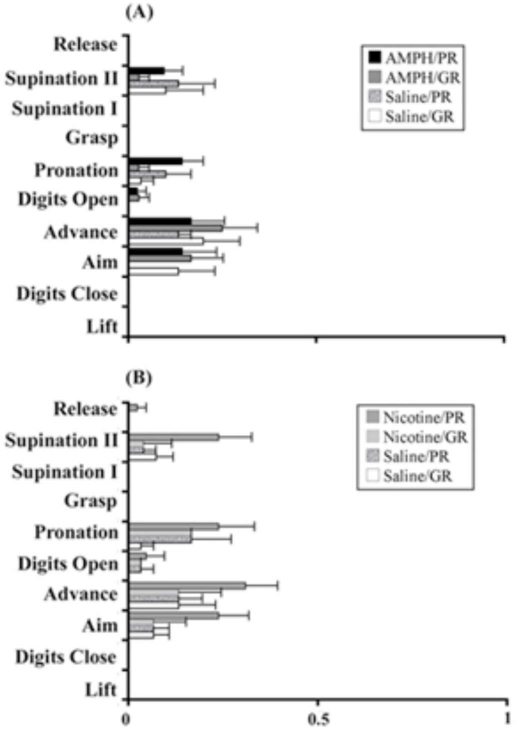


Figure 4.8. Movement elements of reaching on the last day of testing in subgroups of animals with good and poor reaching skills (mean ± *SEM*). (A) AMPH vs. saline group, and (B) Nicotine vs. saline group.

difference between subgroups ($F_{3,19} = 2.271$, $p > 0.05$), but there was a significant effect of element ($F_{9,171} = 11.623$, $p < 0.001$) and a subgroup by element interaction ($F_{27,171} = 1.795$, $p < 0.05$). Post hoc analysis ($p < 0.05$) of the elements within subgroups showed that nicotine-treated PR rats were impaired significantly on supination-II relative to the other subgroups (Figure 4.8.B).

Gesture analysis

Reaching performances on the last test session were analyzed and the number of gestures was calculated for the first five trials. In both studies, the repeated measures ANOVA indicated no significant effect of group (AMPH vs. saline: $F_{1,21} = 1.460$, $p > 0.05$); NIC vs. saline: $F_{1,21} = 0.780$, $p > 0.05$), gesture (AMPH vs. saline: $F_{4,84} = 0.984$, $p > 0.05$); NIC vs. saline: $F_{4,84} = 0.758$, $p > 0.05$), and also no group by gesture interactions (AMPH vs. saline: $F_{4,84} = 0.717$, $p > 0.05$); NIC vs. saline: $F_{4,84} = 0.572$, $p > 0.05$).

However, the repeated measures ANOVA on the number of gestures between subgroups of the AMPH vs. saline group indicated that there was a significant effect of subgroup ($F_{3,19} = 3.677$, $p < 0.05$), but no effect of gesture ($F_{4,76} = 0.936$, $p > 0.05$), and no gesture by subgroup interaction effect ($F_{12,76} = 0.474$, $p > 0.05$). Post hoc analysis ($p < 0.05$) revealed that the AMPH-treated PRs significantly made higher number of gestures relative to the GR subgroups.

No significant difference was found between subgroups of the nicotine study on the number of gestures ($F_{3,19} = 2.493$, $p > 0.05$). Also the effect of gesture ($F_{4,76} = 0.781$, $p > 0.05$) and the gesture by subgroup interaction effect ($F_{12,76} = 0.994$, $p > 0.05$) was not significant. Furthermore, gesture analysis and correlations indicated that the number of

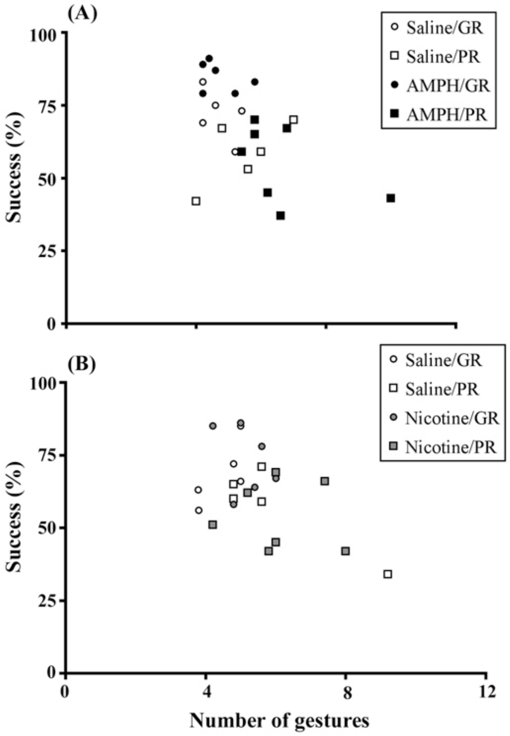


Figure 4.9. Correlation between incidence of gestures and total success. (A) AMPH vs. saline group, and (B) Nicotine vs. saline group.

gestures used per reach were negatively correlated with reaching success in the amphetamine group (r_{12} = - 0.738, p = 0.004)[Figure 4.9.A], but not in the nicotine group (r_{12} = - 0.383, p > 0.05) [Figure 4.9.B].

Discussion

Amphetamine and nicotine are proposed to have efficient roles in promoting recovery of function after stroke. The present study was designed to examine whether the beneficial and activating effects of amphetamine and nicotine and also their potential effects on brain plasticity extend to normal motor function of adult rats without injuries. The main objective of the present study was to investigate the potential effects of prior repeated exposure to amphetamine or nicotine on acquisition of skilled reaching behavior and individual differences following learning single pellet reaching task.

The results indicated that the development of behavioral sensitization following repeated daily injections of the amphetamine (first study) or nicotine (second study) prior to skilled reach training was not beneficial in learning the task or the reaching performance of the sensitized animals. Drug-treated (AMPH or NIC) and saline-treated groups both learnt the task in similar timeframe and endpoint scores. Both drug groups reached similar success rate, single reach success and number of attempts in comparison with the saline groups during training and testing periods.

Comparing the subgroups (GRs and PRs) of the drug-treated vs. saline-injected animals showed that amphetamine had a positive effect only on the GR group with increasing the number of successful reaches. Results of the second experiment indicated that nicotine increased the number of attempts displayed by the GRs and diminished the difference between the GR and PR groups on this measure.

Comparisons of the movement elements between drugs vs. saline groups showed that reaching elements in AMPH-treated animals were not different than the saline group, but NIC-treated rats were impaired on aim, advance and supination in their reaching performance in comparison with the saline-treated group. The PRs in the nicotine group showed a higher impairment on rotatory movement (supination II) compared with the other groups. The present results suggest that prior repeated exposure to amphetamine or nicotine, which led to behavioral sensitization, did not have beneficial effects on acquisition and performance of single pellet reaching but each drug had different effects on skilled reaching performance of subgroups of animals with good and poor reaching skills.

The present experiments were designed to investigate the role of induced behavioral sensitization via prior intermittent exposure to amphetamine or nicotine on the acquisition and performance of skilled reaching of the normal adult rats in becoming good or poor reachers. Behavioral sensitization in the present experiments was induced via injection of amphetamine or nicotine according to a well-established model used in previous studies (Bevins & Palmatier, 2003; Domino, 2001; Hakan & Ksir, 1988; Kosowski & Liljequist, 2005; Mendez et al., 2009; Robinson & Becker, 1986; Stewart & Badiani, 1993; Vanderschuren & Kalivas, 2000; Vezina, McGehee, & Green, 2007).

The single pellet task was chosen for two reasons. First, it is a standard task and widely used in the assessment of motor performance. Second, it is a task in which individual differences in skilled reaching are readily observable and measurable (Gholamrezaei & Whishaw, 2009; Metz, Jadavji, & Smith, 2005). This task provides end-point measures of reaching performance and also allows examination of the kinematic aspects of the movement elements used for reaching from frame-by-frame inspection of the video records.

The results obtained from the first phase of the experiments showed that both amphetamine and nicotine produced behavioral sensitization in rats. Behavioral sensitization induced by repeated administration of drug is thought to be effective in improving the behavioral function (Feeney & Sutton, 1987; Goldstein, 2003; Maling & Acheston, 1946; Martinsson, Hardemark, & Wahlgren, 2003) and neuroplastic responses (Ramic et al., 2006; Robinson & Kolb, 1997; Stroemer, Kent, & Hulsebosch, 1998). Because of the long-lasting effects of behavioral sensitization (Paulson, Camp, & Robinson, 1991; Paulson & Robinson, 1995; Robinson & Becker, 1986), the enhancement of motor function was examined in later skilled reaching performance of sensitized vs. non-sensitized rats. The results indicated that prior repeated exposure to amphetamine or nicotine did not improve subsequent acquisition and performance of single pellet reaching.

The beneficial effects of amphetamine and nicotine on recovery of function after stroke have been reported previous studies. For example, some studies have shown that administration of amphetamine or nicotine improves postural balance and coordinated limb use in locomotion or skilled reaching in a time-dependent manner or in combination with rehabilitative training after stroke (Adkins & Jones, 2005; Goldstein, 2003; Gonzalez, Gharbawie, & Kolb, 2006; Hovda & Fenney, 1984; Ramic et al., 2006), but the efficacy of these treatments depends on several factors such as the dose of drug, timing schedule, behavioral requirements of the task, and also combination of drug and physical rehabilitation after brain damage (Adkins & Jones, 2005; Barbay et al., 2006;

Ramic et al., 2006; Schmanke, Avery, & Barth, 1996). However, there are some other studies in which no recovery of function and motor improvements were found as a result of amphetamine or nicotine administration after brain damage (Alaverdashvili, Lim, & Whishaw, 2007; Lim, Alaverdashvili, & Whishaw, 2009; Platz et al., 2005). Therefore, these drugs can be useful in enhancing motor function in limited circumstances.

Present findings suggest that the efficacy of amphetamine or nicotine to facilitate motor function also depends on the individual differences in developing skilful movements. Consistent with previous accounts, saline-injected control GRs showed better reaching skills with higher success scores and lower number of attempts relative to the saline-treated PRs. However, pretraining exposure to amphetamine had different effects on animals in developing the good vs. poor reaching skills but not as expected. It has been suggested that GRs and PRs might develop different learning strategies in acquisition of skilled reaching behavior (Gholamrezaei & Whishaw, 2009). The GRs display goal-directed behavior and rely on a goal strategy in which direct their hands to the appropriate spatial locations of the food, whereas, the PRs develop a stimulus-response approach to the task that makes them prone to develop motor habits. That is consistent with other reports that there are individual differences in developing approach strategy and habitual responses (Boakes, 1977; Flagel, Clinton, Watson, Robinson, & Akil, 2007; Flagel, Watson, Akil, & Robinson, 2008; Hogarth & Chase, 2011; Robinson & Flagel, 2008). Previous studies have shown that sensitization to amphetamine disrupts the acquisition of goal-directed actions, enhances the formation of stimulus-reward associations and accelerates the progression of habitual responding (Hitchcott, Harmer, & Phillips, 1997; Nelson & Killcross, 2006; Taylor & Jentsch, 2001). Thus, it was expected that sensitization induced by prior amphetamine administration would affect animals in becoming more poor reachers rather than good reachers. The findings suggest somewhat different than that was expected. Results showed that sensitization with amphetamine improved successful performance of skilled reaching in the GRs but no differences were found between skilled reaching performances of the sensitized- and non-sensitized PRs. Unfortunately, the design of the experiments did not allow us to investigate individual differences in skilled reaching prior to the behavioral sensitization and the comparisons were made based on the performance of non-sensitized counterparts.

Nicotine sensitization had a detrimental effect on the GRs reaching skills through increasing the number of attempts. Prior exposure to nicotine diminished the difference on the number of attempts between the GRs and PRs. Although the movement elements such as aim, advance, and supination were impaired in nicotine-treated animals but the increase of the number of attempts in the GR group is unlikely due to their abnormal movements. Previous studies have shown that nicotine-treated animals showed impairments in learning a new task such as single pellet reaching task with lower success rates and movement element impairments due to premature plastic changes induced by nicotine (enhanced dendritic branching and length of pyramidal cells in the motor cortex), which might interfere with normal learning (Gonzalez, Gharbawie, & Kolb, 2006). In addition, it has been found that administration of nicotine prior to enriched environment such as complex housing blocks the increase of experience-dependent dendritic arborization, length, and spine density induced by enriched environment (Hamilton & Kolb, 2005). Therefore, the impairments of movement element found in the present study might be related to the interference of nicotine with normal experience-dependent plasticity.

In conclusion, despite the general activating effects of amphetamine and nicotine and their effects on neural plasticity (Brown & Kolb, 2001; Meintzschel & Ziemann, 2006; Robinson & Kolb, 1997, 2004; Singer et al., 2009), induced behavioral sensitization by repeated administration of these drugs did not promote acquisition and performance of single pellet reaching. Present results are in line with previous studies and support the idea that the skilled reaching is resistant to pharmacotherapy (Lim, Alaverdashvili, & Whishaw, 2009). Although amphetamine and nicotine improve some aspects of motor behavior after stroke, these drugs similar to other treatment such as levodopa (Melwin et al., 2005; Metz, Farr, Ballermann, & Whishaw, 2001) and fluoxetine (Windle & Corbett, 2005) do not enhance skilled reaching performance. However, subgroups of sensitized animals to amphetamine or nicotine developed better or worse reaching skills relative to non-sensitized animals. Amphetamine was more effective on skilled reaching in a group of animals that developed good reaching skills but not in poor reachers. On the other hand, nicotine not only had no positive effect on skilled reaching but also it was detrimental. Therefore, although each of these treatments might be effective in a specific population or on particular aspects of behavior, they are not effective for the enhancement of skilled reaching performance in general.

CHAPTER 5

Role of the motor cortex in the individual differences in skilled reaching for food: Good reaching skills depend on the motor cortex

Abstract

Post-stroke behavioral outcomes and the patterns of recovery in human and non-human animals are widely variable and cannot easily be predicted. Although there are several investigations on the effects of stroke type and lesion size on the variability in the behavioral outcome and recovery of function, the role of individual differences in motor performance has not been described as a source of post-stroke behavioral heterogeneity. Rats were trained in single pellet reaching task and divided into two groups of good and poor reaching skills prior to a small motor cortex stroke. Following motor cortex injury, skilled reaching performance was assessed during acute and chronic recovery periods and compared to pre-lesion performance. The results indicated that small motor cortex lesions via pial removal produced a mild behavioral deficit only in animals with good reaching skills. Rats with good reaching skills displayed a decrease in successful reaching (both total success and single reach success) and also increased number of attempts, whereas the poor reachers did not show significant changes in any of the end-point measures. However, both groups were impaired in the way they performed reaching movements during the acute post-lesion period. The findings are discussed in relation to the idea that skilled reaching variability after a small motor cortex damage might be related to the differences in the neural processes underlying skilled reaching behavior used by different groups of animals.

Introduction

Post-stroke behavioral outcomes and recovery patterns in human and non-human animals are widely variable and cannot easily be predicted. This variation displayed by animals is more obvious during early postsurgical period (Whishaw, 2000). Different factors such as stroke type (Alaverdashvili, Moon, Beckman, Virag, & Whishaw, 2008; Voorhies & Jones, 2002; Woodlee et al., 2005), infarct size and location (Gonzalez & Kolb, 2003; Whishaw, 2000), age (Brown, Marlowe, & Bjelke, 2003; Sutherland, Dix, & Auer, 1996), sex (Gargano & Reeves, 2007; Zalihić, Markotić, Zalihić, & Mabić, 2010), and genetic susceptibility (Carr et al., 2002; Waters & Nicoll, 2005) may contribute to the rate of behavioral recovery. It is interesting that a substantial variability has been reported even within a single stroke type, size and location. For example, Whishaw (2000) reported a large variation in the skilled reaching performance of individual animals across and within days during early post-surgical period. Also, Metz et al. (2005) reported less motor impairment with an increased number of successes in a subgroup of animals after photothrombotic motor cortex stroke. Another report by Erickson et al. (2007) showed individual differences in susceptibility to diaschisis in acute period following motor cortex devascularization.

Understanding factors influencing recovery of function after brain injuries may provide insights into how brain reorganizes itself after stroke, how recovery can be improved or delayed and how a particular treatment might be useful. Although there are several investigations on the role of stroke type and lesion size and their effects on recovery of function, there is a lack of systematic examination of individual differences as a source of post-stroke behavioral heterogeneity. This was the focus of the present study. Rats display considerable variation in normal skilled reaching behavior (Gholamrezaei & Whishaw, 2009). The variable rates of motor recovery in rats' skilled reaching after stroke raise a question of whether the source of variability is related to individual differences in skilled reaching of the rats prior to stroke.

The purpose of the present study was to investigate the acute and chronic effects of a small motor cortex lesion produced by pial removal on skilled reaching behavior by comparing groups of rats with good and poor reaching skills. The standard training procedure (Whishaw & Pellis, 1990) was used to train animals in skilled reaching task prior to the small motor cortex injury. Then rats were divided into two groups with good and poor reaching skills based on end-point measures of their performance. After a motor cortex lesion to the caudal forelimb area, animals' skilled reaching performance was evaluated over 21 consecutive days. In addition, a detailed analysis of limb movement elements (Whishaw, Dringenberg, & Pellis, 1992; Whishaw, Pellis, Gorny, & Pellis, 1991) was used to assess functional improvements following lesion-induced deficits. Movement element scores derived from frame-by-frame video movement assay as described with Eshkol-Wachmann Movement Notation (EWMN; Eshkol & Wachmann, 1958).

Method

Subjects

The subjects were 12 female Long-Evans rats, 3 months old and weighing 200-300 g at the beginning of the experiment. The animals were housed in standard Plexiglas cages in an animal colony room with food and water available and a 12h light-dark cycle (lights on 7:30-19:30h). The room temperature maintained at 22° C. The experiments were in compliance with the guideline of the University of Lethbridge animal care committee and the Canadian Council for Animal Care, which complies with international standards for animal care.

Food restriction

The animals were gradually food deprived to 90-95% of their normal body weight prior to and during training. Each rat received 15g of Puria rat chaw once a day to maintain at that body weight. Also they received 0.9g of 45 mg dustless precision banana-flavored pellets (product# F0021, Bioserve Inc., Frenchtown, NJ, USA) for 3 days prior to initial training on the single pellet-reaching task for familiarization with the taste and smell of the food pellets. During the training and testing sessions, the banana-flavored pellets were served only as targets in the reaching task. Each animal could receive up to 20 pellets per day depend on the reaching accuracy.

Single pellet reaching box

The single pellet-reaching box was made of transparent Plexiglas with 45 cm length, 14 cm width, and 35 cm height. In the middle of the front wall, a 1 cm wide slit is extended from bottom of the box to a height of 15 cm. A 2 cm wide by 4 cm long shelf is attached to the outside of the front wall, 3 cm above the bottom of the box in front of the opening. There are two small indentations with 1.5 cm distance from the front wall aligned with each side of the slot to hold the food pellets. A food pellet in each indentation is accessible only to the contralateral forelimb, because it pronates medially to grasp (Whishaw & Pellis, 1990).

Training

Reach training sessions were conducted at approximately the same time each day in a testing room. Rats were trained on the single pellet-reaching task for 14 days. On the first day of training, rats were placed individually in the reaching apparatus with pellets on the shelf for 10 minutes. Once the pellets were retrieved successfully, the pellets were moved further away on the shelf to encourage the rat to use a hand and reach for the food. Pellets were initially presented in both indentations to determine the dominant forelimb. Once a rat showed a clear preference for one hand, by making more reaching attempts with it, a single food pellet was presented in the indentation contralateral to the preferred forelimb. In order to obtain discrete reaching trials, rats were required to reposition their body on each trial. They were shaped to leave the slot, walk to the rear wall of the box, turn and approach the slot again for the next pellet. In addition, by withholding food on semi-randomly selected trials, rats were taught to sniff the shelf for a pellet and to reach only if a pellet was present. Single pellet reaching tests (each session consisted of 20 trials) were performed for five consecutive days after the completion of the training sessions.

Video recording

Video records were made using a Sony 3CCD camcorder with a shutter speed of 1000th of a second. Illumination for high shutter speed filming was provided by a cold light source (Whishaw & Pellis, 1990). Frame by frame analysis was done at 30 frames per second using a Sony digital videocassette recorder DSR-II.

Motor cortex devascularization

Small motor cortex lesions were made in the caudal forelimb area of the sensorimotor cortex (Donoghue & Wise, 1982; Hall & Lindhom, 1974). The lesion was performed on the side contralateral-to-the pretrained forelimb. To facilitate respiration throughout surgery, the animals received an injection of atropine methyl nitrate (0.1 mg/kg i.p; Sigma-Aldrich, St. Louis, MO, USA) and also they received an injection of analgesic buprenorphine (0.01 mg/kg s.c; Schering-Plough, Hertfordshire, UK) prior to the surgery. They were then anesthetized with sodium pentobarbital (45 mg/kg, i.p; Sigma-Aldrich, St. Louis, MO, USA). The skull was removed by drilling four holes into the skull overlaying the motor cortex and demarcating the lesion target. The stereotaxic coordinates as measured from Bregma were anterior (A) and lateral (L): A +0.5 mm, L -2.0 mm; A +0.5 mm, L -3.5; A +2.0 mm, L -3.5 mm; A +2.0 mm, L -2.0 mm. The exposed dura matter was cut, peeled away and the tissue was devascularized by gently removing the pia matter and blood vessels using a saline-soaked cotton swab. The incision was sutured and the animal was received a second dose of buprenorphine (0.01 mg/kg s.c.). The animals were monitored during 24 h recovery time before being returned to the colony room.

Behavioral analysis

End point measures

A testing session consisted of twenty trials. On each trial, the rat had to approach the slot from the back of the box, reach for the food pellet through the slot, and after attempting to gain the food (grasping the food or else knocked it off the shelf), return to the rear of the box. Reaching performance was analyzed and for each trial the number of attempts, first reach success and total success were recorded (Whishaw, 2005; Whishaw, Dringenberg, & Pellis, 1992).

Attempt. The number of reach attempts was counted in each trial of five pre-lesion testing sessions. A reach attempt is defined as a forward movement of rat's preferred forelimb through the slot in the front wall of the reaching box in an attempt to grasp and obtain the food. A reach attempt could be successful or not depending on the accuracy of the reaching movement.

First reach success. First reach success is defined as a reach attempt in which the food pellet is grasped with the first advance of the forelimb and is consumed by the rat. First reach success scores were calculated as follows:

First reach success (%) = (Number of first reach successes/ Number of trials) × 100

Total success. Success is defined by reaches resulted in obtaining food by grasping the pellet with the hand despite the number of reach attempts. Total success percent was calculated as follows:

Total success (%) = (Number of successes/ Number of trials) × 100

Movement element analysis

Reaching movements were analyzed using a rating scale derived from Eshkol-Wachmann Movement Notation (EWMN) analysis of reaching (Eshkol & Wachmann, 1958; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993) based on the analysis of the relations and changes of relations between the body parts involved in the reaching movement. A reach was subdivided into ten reaching elements including; *(1) Digits to the midline:* The reaching limb is lifted from the floor so that the tips of the digits are aligned with the midline of the body. *(2) Digits closed:* As the limb is lifted, the digits are flexed and closed, the hand is supinated and the wrist is partially flexed. *(3) Aim:* The forelimb and elbow are carried inward to the midline of the body, with the hand located just under the mouth. *(4) Advance:* The limb is advanced directly through the slot toward the food pellet. *(5) Digits extend:* During the advance, the digits extend toward the food pellet. *(6) Arpeggio:* When the hand is over the food pellet, it pronates from digit 5 through to digit 2, and at the same time the digits open. *(7) Grasp:* The digits close and flex over the food pellet, with the hand remaining in place, and the wrist is slightly extended to lift the food. *(8) Supination I:* As the hand is withdrawn, it supinates by almost 90°. *(9) Supination II:* Once the hand is withdrawn from the slot to the mouth, it supinates further by about 45° to place the food pellet in the mouth. *(10) Release:* The mouth contacts the hand and the digits open to release the food pellet.

Ten reaching elements were analyzed and scored for first three successful reaches of the last presurgery session, and also post-surgery days of 5, 15, and 21. Each of the reaching elements was rated on a three-point scale. A score of “0” was given for a normal movement, a score of “0.5” for an abnormal movement, and a score of “1” for the absence of a movement (Piecharka, Kleim, & Whishaw, 2005; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993).

Histology

At the completion of the experiments, animals were euthanized with an overdose of sodium pentobarbital and intracardially perfused with 0.9% phosphate buffered saline followed by a 4% paraformaldehyde solution. The brains were removed from the skull post-fixed and cryoprotected in a 30% sucrose and 4% paraformaldehyde solution. Coronal sections (40 μm) were cut throughout the brain on a cryotome, mounted on the gelatine-coated slides and stained with 0.3% Cresyl Fast Violet for the lesion analysis. Digital images were captured from three different coronal sections from the rostral, middle, and caudal extent of the lesion. The ImageJ program (V 1.36 http://rsb.info.nih.gov/ij/download.html) was used to estimate the tissue loss of the motor cortex damage by comparing the remaining tissue area with that in the undamaged tissue of the intact hemisphere (ipsilateral-to-the- pretrained limb). The following formula was used to estimate the tissue loss (%):

Tissue loss (%) = [ipsilateral motor cortex (pixels^2) – contralateral motor cortex (pixels^2) / ipsilateral motor cortex (pixels^2)] × 100

Statistical analysis

The animals were divided into two groups according to their single reach success scores during last five days of training (Gholamrezaei & Whishaw, 2009). Animals above the median of this rank order were assigned to the GR group, whereas the animals below the median were assigned to the PR group. The results and comparisons between groups were made using multivariate and repeated measures analysis of variance (ANOVA). Follow-up analyses of significant interactions were performed with Bonferroni post hoc tests. Also, comparisons of means between groups were performed using paired and unpaired *t*-tests. In all statistical analyses, a *p*-value of less than or equal to 0.05 was considered significant. All results were presented as mean ± the standard error of the mean (SEM).

Procedure

After pretraining in the single pellet-reaching task, the animals underwent surgery. The recovery of skilled reaching was examined for 21 consecutive days (20 trials each day) starting from the next day after the motor cortex lesion. End-point measures were assessed daily and movement element analysis was made on the day before motor cortex lesion, post-lesion day 5, day15, and day 21.

Results

Histology

Figure 5.1 illustrates a dorsal image of the brain from a representative rat that had received a small motor cortex lesion and also coronal sections from the rostral, middle, and caudal extent of the representative brain lesion. The mean percentage of tissue loss on contralateral forelimb region of the motor cortex was 34.87 $\pm$ 4.05 *S.E.M.* % of the intact forelimb motor area in the ipsilateral hemisphere.

To determine whether motor cortex infarct size affected the behavioral measures, the estimated percentage of tissue loss in the lesion-hemisphere was correlated with post-surgical end-point measures (Figure 5.2). Consistent with a previous report (Whishaw, 2005) no significant correlations were found between the tissue loss and total success ($r_{(11)}$= -0.347, $p > 0.05$) (Figure 5.2.A), single reach success ($r_{(11)}$= -0.442, $p > 0.05$) (Figure 5.2.B), or the number of attempts ($r_{(11)}$= 0.483, $p > 0.05$) (Figure 5.2.C). Also tissue loss (%) was compared between animals with good vs. poor reaching skills and the results indicated no significant difference between groups ($F_{(1,10)} = 0.534$, $p > 0.05$). The mean percentage of tissue loss in the good reachers was 31.85 $\pm$ 5.85 *S.E.M.* and in the poor reachers was 37.90 $\pm$ 5.85 *S.E.M.* (Figure 5.3).

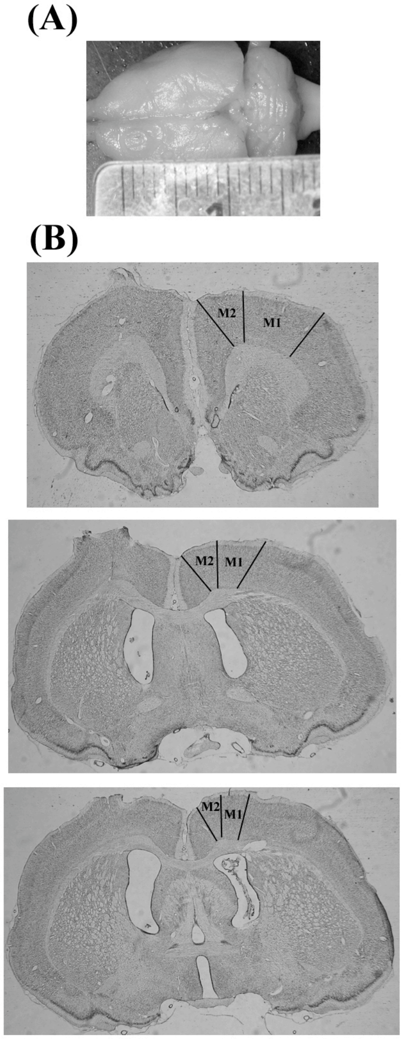


Figure 5.1. Representative small forelimb motor cortex stroke. (A) dorsal image of a post-fixed brain with unilateral devascularization lesion of the motor cortex. (B) coronal sections from the rostral, middle, and caudal extent of the representative lesion. Note: Cortical tissue surrounding the lesion penetrated into the cavity.

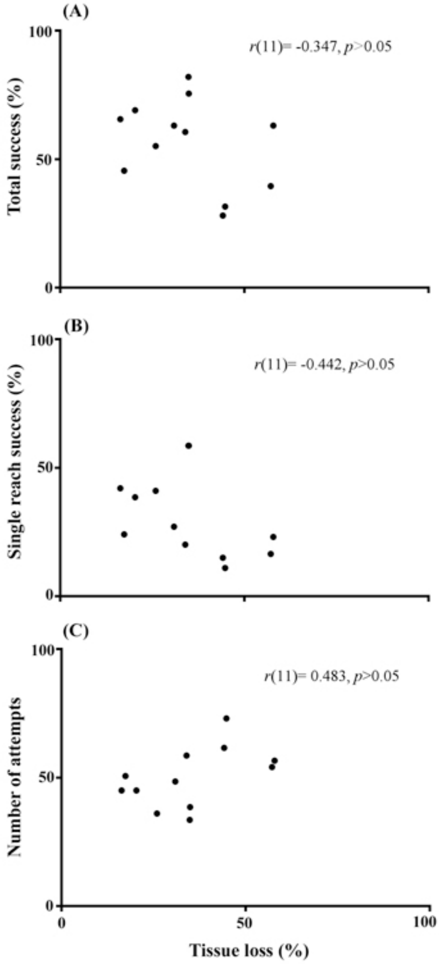


Figure 5.2. Correlation between endpoint scores and tissue loss (%). (A) total success (%), (B) single reach success (%), and (C) number of attempts.

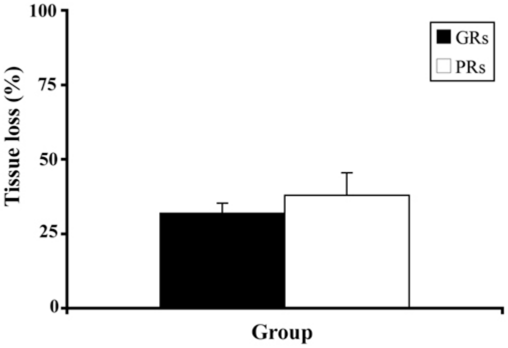


Figure 5.3. Percentage of tissue loss in animals with good vs. poor reaching skills.

Single pellet reaching

End point measures

(1) *Total success.* Success rates were measured for 5 days of pre-surgery training days and also 21 post-surgery test sessions and analyzed as pre-lesion, first 10 days of post-lesion, and last 11 days of post-lesion mean scores. A summary of pre- and post-lesion success scores is illustrated in Figure 5.4.A. The small motor cortex lesion significantly alters the total reaching success ($F_{(2,20)} = 3.712$, $p < 0.05$). No significant difference was found between groups ($F_{(1,10)} = 3.186$, $p > 0.05$), and also no interaction of group and test day was found ($F_{(2,20)} = 1.866$, $p > 0.05$). Post hoc analysis indicated a significant difference ($p < 0.05$) between pre- and first 10 days of post-lesion performance only. It is interesting that the lesion effect diminished the pre-lesion difference on the success scores between groups. Examining the effects of lesion within groups showed that decline of the total success scores was only significant for the animals with good reaching skills.

(2) *Single reach success.* Pre- and post-lesion single reach success scores are shown in Figure 5.4.B. The small motor cortex lesion reduced single reach success scores markedly compared to pre-lesion performance ($F_{(2,20)} = 7.842$, $p = 0.003$). Also a significant difference was found between groups ($F_{(1,10)} = 9.045$, $p < 0.05$), but no interaction ($F_{(2,20)} = 1.702$, $p > 0.05$). Post hoc analysis revealed significant difference ($p < 0.05$) between pre- and post-lesion performance (both first 10 days and last 11days). Examining the effects of small motor cortex lesion within groups revealed that the reduction of single reach success scores was dominant in the good

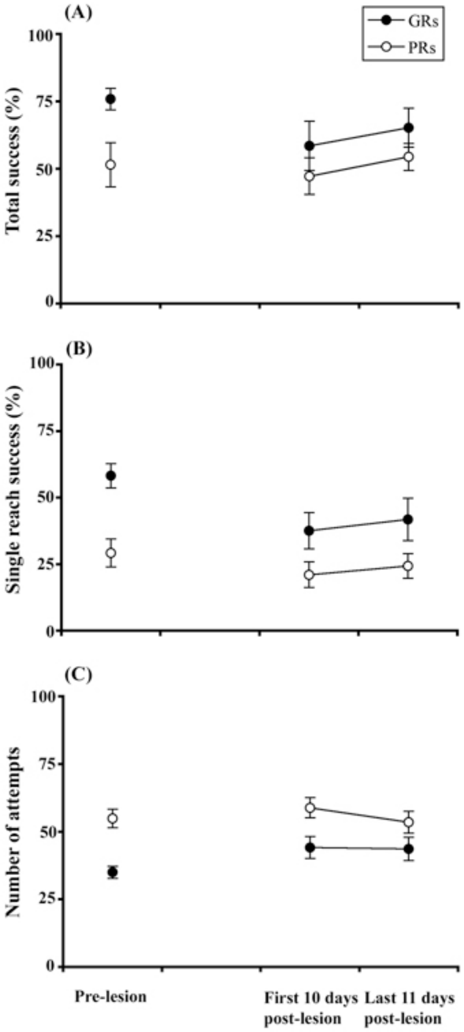


Figure 5.4. Pre- and post-lesion endpoint scores of skilled reaching performance (mean ± *SEM*). (A) total success (%), (B) single reach success (%), and (C) number of attempts.

reachers. The reduction of single reach success scores was not significant in the rats with poor reaching skills.

(3) *Number of attempts.* Pre- and post-lesion performance on the number of attempts is illustrated in Figure 5.4.C. A significant increase in the number of attempts was found between pre- and post-lesion days ($F_{(2,20)} = 4.541$, $p < 0.05$). Also a significant difference was found between groups ($F_{(1,10)} = 10.390$, $p = 0.009$), but no interaction of group and test day ($F_{(2,20)} = 2.441$, $p > 0.05$). Post hoc analysis revealed a significant increase of attempts during first 10 days but not last 11 days of post-lesion ($p <0.05$). Also examination of the effects of lesion within groups indicated that the increased number of attempts was only significant in the GR group. Although the number of attempts increased in the poor reachers performance after lesion but no significant difference was found when compared with pre-lesion performance.

Pattern of successful reaches

The number of different types of successful reaches before and after lesion is shown in Figure 5.5. Results indicated that after motor cortex lesion single reach success scores (Figure 5.5.A) decreased significantly ($F_{(2,20)} = 7.778$, $p = 0.003$). Although no difference was found between the first and last 10 days of post-lesion on single reach success, both were significantly different when compared to the pre-lesion performance. The single reach success scores after lesion in the PR group did not differ when compared to the pre-lesion performance. A significant difference was found only in the performance of the GR group. The reduction of the single reach success in this group did not change the difference between groups and the level of single reach success

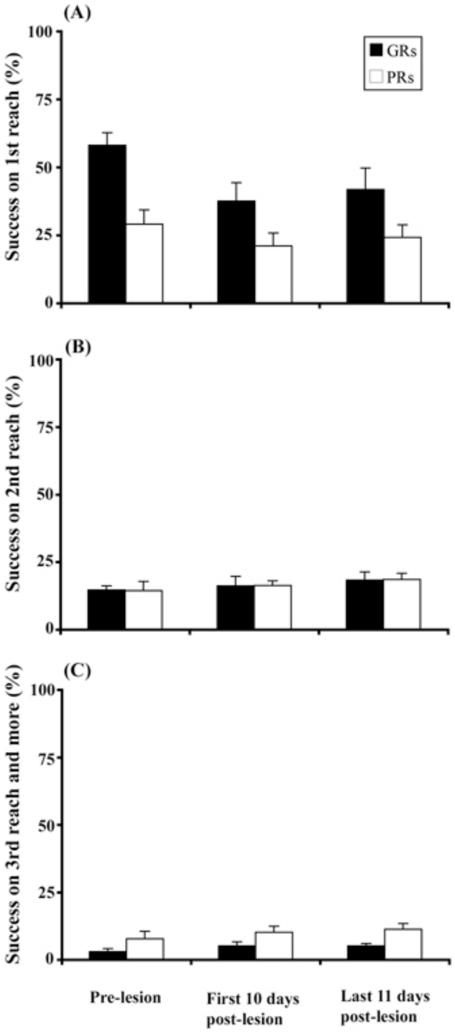


Figure 5.5. Patterns of successful reaches (mean ± *SEM*). Note: The reduction of single reach success scores and increase of success scores on more than 3 consecutive reaching attempts are noticeable.

was still significantly higher in the GR group after motor cortex lesion ($F_{(1,10)} = 9.224$, $p = 0.013$), also no interaction of group by test day was found ($F_{(2,20)} = 1.679$, $p > 0.05$).

The success scores on the 2nd reach (Figure 5.5.B) did not differ after motor cortex lesion ($F_{(2,20)} = 2.230$, $p > 0.05$), and no difference was found between groups ($F_{(1,10)} = 0.001$, $p > 0.05$). Also no interaction of group by test day was found ($F_{(2,20)} = 0.009$, $p > 0.05$).

Results on success made by more than 3 reaching attempts (Figure 5.5.C) revealed that this type of success increased after motor cortex lesion during both first and last 10 days of post-lesion ($F_{(2,20)} = 9.194$, $p = 0.001$). A marginal difference was found between groups ($F_{(1,10)} = 4.493$, $p = 0.06$). Also no interaction of group by test day was found ($F_{(2,20)} = 0.517$, $p > 0.05$). The increased number of success on 3rd reach and up was observed in both groups. The success on 3rd and more reaching attempts in the GR group during both first and last 10 days of post-lesion were significantly different compared to the pre-lesion performance but this type of success increased significantly only during the second half of the post-lesion period in the PR group.

Correlation analysis of pre- vs. post-lesion reaching performance

Correlations between pre- and post-lesion endpoint measures are illustrated in Figure 5.6. The correlation analysis revealed that there was a significant correlation between pre- and post-lesion behavioral measures, Total success ($r_{(11)} = 0.675$, $p < 0.05$) (Figure. 5.6.A), single reaching success ($r_{(11)} = 0.677$, $p < 0.05$) (Figure 5.6.B), and the number of attempts ($r_{(11)} = 0.691$, $p < 0.05$) (Figure 5.6.C).

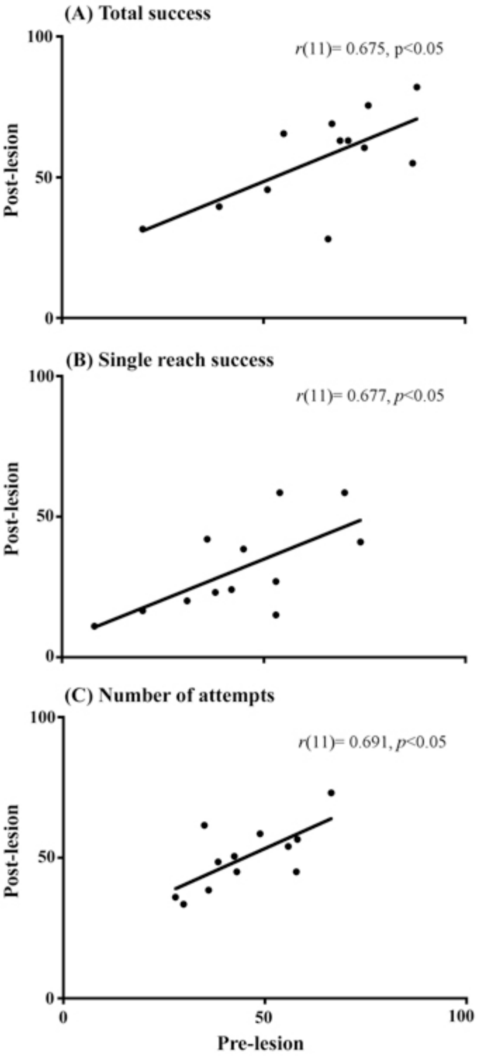


Figure 5.6. Correlation between pre- and post-lesion endpoint measures.

Movement elements

Separate analyses were performed for four scoring days including pre-lesion day, post-lesion day5, day15, and day21. A summary of pre- and post-lesion reaching movement element scores for the GR and PR groups are illustrated in Figure 5.7. The movement element analyses indicated that there were no significant differences on movement elements between GRs and PRs prior to- or after the motor cortex lesion (pre-lesion: $F_{(1,10)} = 0.061$, $p > 0.05$; post-lesion day5: $F_{(1,10)} = 0.00$, $p > 0.05$; day15: $F_{(1,10)} = 0.011$, $p > 0.05$; day21: $F_{(1,10)} = 0.122$, $p > 0.05$). Following the small motor cortex lesion the animals in both groups were similarly impaired on a number of movement elements such as aim, advance, supination II, and release.

In order to determine whether there was a rehabilitation effect on the reaching elements, pre-lesion performance compared to the performance during acute (post-lesion D5) and chronic (post-lesion D15 and D21) periods. Results indicated that the pattern of impairment changed through different periods after the lesion. For example, aim ($F_{(3,30)} = 6.942$, $p < 0.001$) and release ($F_{(3,30)} = 10.367$, $p < 0.001$) were impaired on both post-lesion D5 and D15. Release element recovered in the PRs faster than the GRs. The result confirmed by a day and group interaction effect ($F_{(3,30)} = 3.466$, $p < 0.05$). Supination II ($F_{(3,30)} = 7.391$, $p < 0.001$) was impaired significantly on the acute period D5. Advance ($F_{(3,30)} = 7.278$, $p < 0.001$) and pronation ($F_{(3,30)} = 7.105$, $p < 0.001$) impairments showed up later in time on D15. The pronation impairment was observed only in the PRs and digits open was impaired in the GRs. All movement elements were recovered by the post-lesion D21.

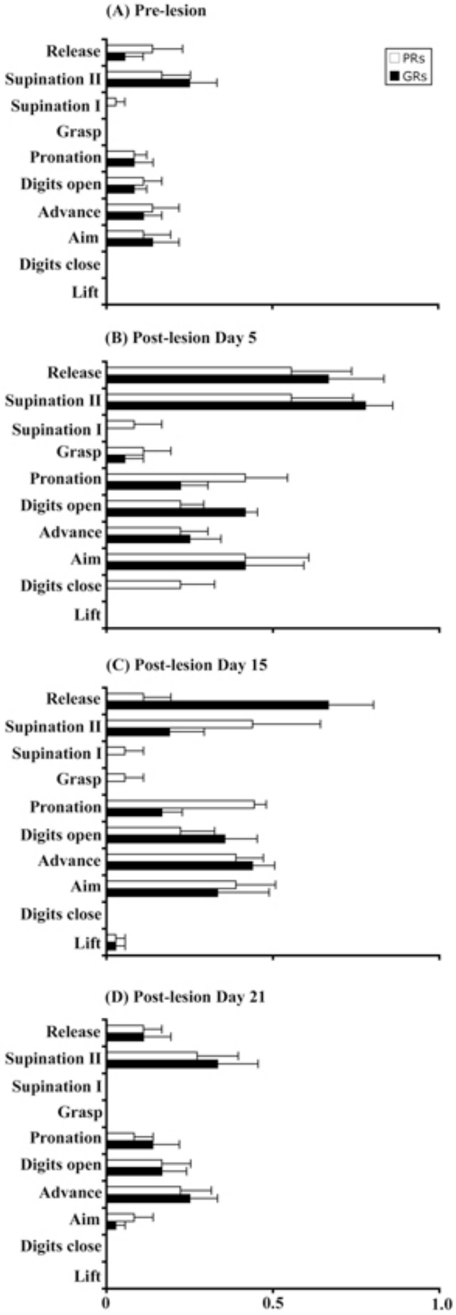


Figure 5.7. Pre- and post-lesion reaching movement element scores in the animals with good and poor reaching skills. (A) pre-lesion movement element scores, (B) post-lesion day5, (C) post-lesion day15, and (D) post-lesion day21. *Note:* All movement elements were recovered by the last test session (post-lesion day 21).

Discussion

The objective of the present study was to investigate the acute and chronic effects of a small motor cortex lesion to the caudal forelimb area and variability of behavioral outcomes in relation to individual differences in skilled reaching behavior prior to the damage. Recovery patterns were examined by comparing two groups of rats with good and poor reaching skills. The performance in the skilled reaching task was assessed by end-point measures of total success, single reach success, and number of attempts prior to the lesion for assigning animals into two groups of good vs. poor reachers. The same end-point measures were reevaluated during acute and chronic periods after the lesion. In addition, limb movement elements were analyzed for functional improvements over recovery days.

The results indicated that small motor cortex lesion via pial removal produced a mild behavioral deficit in a subgroup of animals. Rats with good reaching skills displayed a decrease in successful reaching (both total success and single reach success) and an increased number of attempts, whereas the poor reachers did not show significant changes in the end-point measures of total success, single reach success, and the number of attempts compared to their pre-lesion performance. However, both groups were impaired in the way they performed their reaching movements during the acute post-lesion period. Nevertheless, the rats significantly recovered after three weeks of rehabilitation.

Previous studies on the effects of motor cortex lesion on behavioral outcome indicated large variations in the skilled performance regardless of lesion type, size and location, during the early post-surgical period (Alaverdashvili, Moon, Beckman, Virag, &

Whishaw, 2008; Erickson, Gharbawie, & Whishaw, 2007; Goldstein & Davis, 1990; Knieling, Witte, & Metz, 2003; Metz, Antonow-Schlorke, & Witte, 2005; Napieralski, Banks, & Chesselet, 1998; Whishaw, 2000). Individual differences in pre-surgical performance could be considered as a variable that might influence the behavioral outcome after cortical damage, which was addressed in the present study.

Damaging the caudal forelimb area of the motor cortex was chosen because of its central role in skilled reaching. It has been shown that the caudal area of the motor cortex is most critical for skilled reaching in rats (Gharbawie, Karl, & Whishaw, 2007) and in primates (Friel et al., 2005). Lesions in the caudal forelimb area produced similar reaching deficits compared to the "standard" motor cortex lesion in which both rostral and caudal areas are damaged. In addition, lesions of the caudal motor cortex resulted in larger behavioral deficits when compared to lesions in the rostral region of the motor cortex (Gharbawie, Karl, & Whishaw, 2007).

The behavioral deficits resulting from the small lesion in the present study were mild but they decreased the total success and single reach success without a severe depression of success. The lesion led to increased number of attempts without development of "learned non-use", the tendency to quit using the bad limb (Alaverdashvili, Foroud, Lim, & Whishaw, 2008; Erickson, Gharbawie, & Whishaw, 2007; Taub, 1977; Taub et al., 1993; Whishaw, 2000) or switching forelimb use (Hsu & Jones, 2005; Gonzalez et al., 2004) during early post-lesion period. However, the reaching deficits after a "standard" motor cortex lesion consist of an acute decline of successful reaching, especially single reach success and reaching attempts in early post operative period followed by improvements in performance via compensatory strategies

(Metz, Antonow-Schlorke, & Witte, 2005; Whishaw, 2000; Whishaw, Pellis, Gorny, & Pellis, 1991). The mild end-point impairments found in the present study are likely due to the small lesion size.

It is interesting that the behavioral deficits in total success and number of attempts recovered after three weeks of rehabilitation. The present findings support the idea that chronic reaching deficits are more closely related to the lesion size (Alaverdashvili, Moon, Beckman, Virag, & Whishaw, 2008; Metz, Antonow-Schlorke, & Witte, 2005; Gonzalez & Kolb, 2003; Whishaw, 2000) and recovery is proportional to the sparing of the same cortical areas (Gharbawie, Karl, & Whishaw, 2007). Therefore, in general, the extent of the tissue loss might be the primary factor for the acute and chronic behavioral deficits while the remaining portion of the cortical area might be the main factor for the recovery rate.

The main finding of the present study was that despite of similar sized lesion of the motor cortex, reaching deficits was displayed by subgroup of animals with good reaching skills. The good reachers showed a decrease in successful reaching and also increased number of attempts, whereas rats with poor reaching skills did not display significant changes in the end-point measures relative to their pre-surgical performance. The present findings confirm previous reports that subgroups of animals display different end-point performance after small motor cortex lesions (Metz, Antonow-Schlorke, & Witte, 2005). According to Metz and colleagues (2005) small photothrombosis produced either no end-point deficits or end-point improvements in subgroups of animals, which is not quite similar to the present findings. The distinction might be related to the lesion type or based on the factors defining the subgroups.

One interesting feature was the effect of small motor cortex lesion on single reach success scores. The decline in the single reach success was pronounced in the GRs. The same variability in the single reach success scores between animals after small motor cortex devascularization has also been reported previously (Whishaw, 2000). Success on the first reach is the main measure of the skilful behavior because it is a measure for a more demanding task. The animals with good reaching skills are prominent in performing this type of successful reaching and based on their higher single reach success get assigned as the good reachers. However, the rats with poor reaching skills mainly lack the required precision and thus they normally show a low level of single reach success scores. It seems that the small motor cortex lesion primarily affected this type of success, thus GRs are more prone to lose their capabilities. It is noteworthy that the decline of total success in the animals with good reaching skills abolished the pre-lesion group difference.

By comparing pattern of successful reaches prior to- and after the lesion in both groups, it was found that the small motor cortex lesion increased the number of success on more than three reaching attempts. Therefore, the results suggest that the caudal forelimb area of the motor cortex has a primary role in skilful reaching in rats. Possibly the poor reachers may lack the plastic capacity that underlies high success. This suggestion is in line with the idea proposed by Mittleman and colleagues (1988) that the post-stroke behavioral variation might be related to individual variability in neural organization underlying the behavior (Mittleman, Whishaw, & Robbins, 1988; Galaburda, Rosen, & Sherman, 1990). Previous studies suggest that damage to any part of the motor system including the motor cortex (Castro, 1972a; Gharbawie & Whishaw, 2006; Gonzalez & Kolb, 2003; Whishaw, 2000; Whishaw, O'Connor, & Dunnett, 1986), basal ganglia (Clarke, Ploughman, & Corbett, 2007; Maclellan, Gyawali, & Colbourne, 2006; Pisa & Cyr, 1990; Whishaw, O'Connor, & Dunnett, 1986; Whishaw, Zeeb, Erickson, & McDonald, 2007), pyramidal tract (Castro, 1972b; Piecharka, Kleim, & Whishaw, 2005; Whishaw, Pellis, Gorny, Kolb, & Tetzlaff, 1993), red nucleus (Whishaw & Gorny, 1996; Whishaw, Gorny, & Sarna, 1998), and spinal cord (Ballerman, Metz, McKenna, Klassen, & Whishaw, 2001; McKenna & Whishaw, 1999) can impair skilled reaching for food in rats. Because selective damage to any of these structures only alters the quality of movements and does not completely abolish the skilled reaching, it can be inferred that different neural circuits in the motor system might be involved in such skill. Therefore, it can be concluded that the motor cortex is a critical structure for the precise and skilful movements, and fine motor control of the forelimb and it is the core structure in the underlying neural circuits used by the good reachers in performing the task.

Correlation analysis of the pre- and post-lesion performance indicated that good reachers still performed better than the poor reachers even after motor cortex damage. This conclusion does not discount the important role of the motor cortex in the way each movement element is performed. Impairments of the movement elements after the damage in both groups suggest that the motor cortex is the key structure underlying the movements. The examination of movement element revealed that both groups showed impairments in several elements of reaching such as aim, supination, and release during the acute period after the lesion. The abnormality of movement element was still observed in the advance and pronation during second week after the damage, which suggests the involvement of the compensatory movements and their influence on performing normal movements. The development of compensatory movements after small motor cortex lesions was previously reported in both rats (Metz, Antonow-Schlorke, & Witte, 2005; Whishaw, 2000) and primates (Friel & Nudo, 1998). The present results suggest that although there were some variations in movement element impairments in groups and also different recovery time for different movement elements, the animals in both groups displayed true movement elements recovery after three weeks of rehabilitation. This result is supported by previous studies, which reported restoration of function in human patients after small strokes (Bonita & Beaglehole, 1988; Hendricks, van Limbeek, Geurts, & Zwarts, 2002).

The present results are in line with previous report on changes in qualitative performance in two subgroups of animals (consistent and improved reachers) after small motor cortex lesions (Metz, Antonow-Schlorke, & Witte, 2005). The movement element analysis revealed that both groups were similarly impaired on some elements such as aim, supination II, and release. Also both groups showed impairments on different elements. For example, the good reachers displayed digits extension impairment whereas the poor reachers showed changes in pronation. Severely impaired digit movements in the good reachers were noticeable in two elements, digits extension and release. Although release was impaired in both groups, the good reachers showed a longer duration of impairment. On the other hand, the rotatory elements of the reaching movement, pronation and supination, were markedly impaired in the poor reachers. The supination element of the movement was also impaired in the good reachers but it recovered faster in this group. It is interesting to speculate then, that the compensatory mechanisms underlying recovery in

GR and PR is different (Jones & Schallert, 1994; Kolb, Brown, Witt-Lajeunesse, & Gibb, 2001; Nudo, 1999, 2003; Sanes & Donoghue, 2000).

In conclusion, a small motor cortex lesion via devascularization study produced mild motor impairments. The study indicated that variation in motor deficits during early post-surgical period is related to individual differences in motor performance prior to the damage. The present finding suggests that for a complete assessment of the effects of cortical damage and therapeutic interventions, behavioral assessment in relation to individual differences is useful. Thus, for a better understanding and treatment of the acute and chronic impairments after brain injuries, individual differences need to be considered. Future work should be directed toward investigating the anatomical changes induced by brain damage in relation to individual differences and variations of behavioral outcome in order to find better therapeutic interventions and treatments for the patient with brain injury.

CHAPTER 6

General Discussion

The purpose of this thesis was to characterize individual differences in skilled reaching for food in rats and to examine potential sources of individual differences in brain function. This was achieved by two sets of experiments. The first set of experiments was designed to assess skilled reaching behavior in normal rats during skill acquisition and after the establishment of well-practiced performance. These experiments also examined other behavioral characteristics and neurobiological measures that might correlate with individual differences in performance. In the second set of experiments the potential sources underlying the differences and the distribution of individual differences were examined after two different methods of brain manipulations. Rats were subject to behavioral sensitization by repeated exposure to psychomotor stimulants (amphetamine or nicotine) or they received motor cortex damage.

The main findings of the experiments were as following:

1. Rats displayed distinctive variation in the skilled reaching performance. Some displayed very poor success rates and some displayed very good success rates. Although there were differences in skilled reaching performance on a number of endpoint measures, including success rates, number of attempts, and number of gestures, all animals used normal movement elements and gestures in their performance.
2. Detailed behavioral analysis during initial training indicated that although the act of reaching was developed with similar serial and temporal organization, the individual differences started to emerge as the animals became more practiced.
3. There were no significant correlations between other behavioral or brain measures and individual differences in skilled reaching.

4. Behavioral sensitization induced by repeated administration of the psychomotor stimulant drugs amphetamine and nicotine had a marginal effect on individual differences in skilled reaching.
5. Following small motor cortex lesions there was a drop in reaching success and an increase in reaching attempts. The effect occurred mainly in good reachers. Nevertheless, both poor and good reachers were impaired in the way they performed their reaching movements during the acute post-lesion period.

The findings and other relevant issues will be discussed in the following sections, which will include considerations of the importance of investigating individual differences and the importance of individual differences to brain function.

The "group" is the standard unit of investigation for the interpretation of data in neuroscience, and therefore, in most studies, individual differences are hidden by reports of only the group mean and variance. Nevertheless, the case can be made that the application of research findings to rehabilitation, drug treatment, or other therapeutic interventions could be aided by adequate knowledge of individual differences in performance of a behavior. In an actual clinical setting, a therapeutic intervention deals with individuals and their unique set of abilities and skills. Understanding individual differences helps optimizing preventative and therapeutic care. From a research perspective, individual differences should also provide insights into brain function. At the very least, if damage to a region of the brain results in poor performance of a motor skill, it might be expected that an animal with poor motor skill may in turn have deficiencies in the brain region responsible for that skill. Finally, at a very practical experimental level, understanding individual differences provides insights into the adequacy of an experimental manipulation. The extent to which subjects are poor vs. good may reflect on the adequacy of training and measurement procedures used by an experimenter.

Individual differences are also currency of evolution. Darwin's theory of common descent proposes that individual differences are selected by the environment so that individuals possessing a favored trait successfully reproduce and pass that trait on to their offspring. Therefore, individual differences are the basis of selection. It is not surprising, therefore, that a generalist species such as the rat, displays individual differences in motor behavior. Certainly in studies that have measured individual differences in rats, individual differences are reliably obtained (Gholamrezaei & Whishaw, 2009; Mittleman, 2005; Mittleman, Castaneda, Robinson, & Valenstein, 1986; Piazza, Mittleman, Deminiere, Le Moal, & Simon, 1993; Valenstein, 1969; Whishaw, 2000).

Nevertheless, one problem related to the understanding of individual differences, is that of evaluating the importance of a difference. The present experiments examined individual differences in the performance of a skilled reaching behavior, in which a rat uses a hand to obtain a food pellet for eating. It must be considered that the task is quite artificial. Skilled reaching may not be a behavior that in any important way determines an animal's survival in a natural environment. On the other hand, the task is very useful for understanding the neural basis of skilled forelimb use and for investigating neurological conditions and their treatment. For the latter reason, at least, understanding individual differences can prove useful.

Individual differences in skilled reaching

Over the four experiments performed in the present thesis, the results were very consistent. There was a similar wide distribution of performance with some rats having success levels of about 25% and other rats having success levels of close to 100%. Because a rat had to make a complete trip to the back of the test box and then back to the food source, the best rats required close to 20 trips to complete the 20 trials of each day's testing. The bad rats would have required up to and perhaps more than 40 trips to obtain the same nutrient reward. Assuming that the task was motivating, and all rats always completed the task, the poor performance of some rats seems indeed due to impairment in optimal performance. It can be assumed that expenditure of twice as much energy would be costly and as such would motivate improved performance.

Individual differences are well recognized in many studies of motor behavior. As is reviewed in the introduction, individual variation in motor skill of many different kinds is documented in motor skills research. At the more practical level, it is well recognized that even despite extensive practice, certain individuals excel in motor skill while other remain clumsy. Thus, the finding that rats vary in the skill of reaching for food is not surprising.

One purpose of the first phase of the study was to examine whether individual differences in skilled reaching were robust. To this end, the same rats were given a number of challenges designed to improve their performance. First, they were given extensive overtraining. Were individual differences simply a reflection of inadequate experience, overtraining would be expected to reduce the variability in inter animal performance. Second, the rats were also given further training on a simpler reaching task. Third, they were then returned to the original task. None of these procedures resulted in a lessening of group variability, or for that matter, improved performance. Furthermore, the relative ranking of the rats was not changed by these manipulations, it must be concluded therefore, that individual differences in skilled reaching performance are not related in any simple way to experiential factors.

A second objective of the first studies was to examine the consistency of the measures used to quantify performance. Thus, three measures of performance were used, overall success, first reach success, and number of attempts. High consistency was found between the measures. It was found that the most skilful animals reached with higher overall success levels, higher single reach success, and with the lowest number of attempts. This consistency in the rat skilled reaching performance was replicated in all five studies performed for this thesis. In addition, a trial by trial analysis and an additional analysis across the 20 trials of each day's testing session, and across days of testing consistently showed a consistency in performance in which individual animals displayed little change in their rankings. Thus, the multiple measures used in the study indicated that the measures of performance were robust.

The third objective of the present thesis was satisfied by overall comparison of the first studies, which imply that the sex differences are not a determining variable affecting the performance of good vs. poor reachers. Sex differences are widely reported in motor skills research with males generally excelling in tasks requiring strength and spatial skills and females excelling in tasks that require fine motor skills (Field & Whishaw, 2005). The present study found similarity in functional endpoints in skilled reaching performance in male and female rats. This gender-neutral result suggests that individual differences in skilled reaching are not due to any of the obvious sex-related differences, including differences in the body size of the rats, their morphology, or their hormonal status. In addition, because rats were tested repeatedly over many days, individual differences in motor skill did not appear to fluctuate in any obvious way with the animal's estrous cycle. Previous studies of the skill with which rats can walk on a beam have reported changes in skill with estrous cycle (Becker, Snyder, Miller, Westgate, & Jenuwine, 1987).

A fourth objective of the first studies was to examine whether in coordination or clumsy movements could be related to individual differences in any simple way. An obvious source of poor vs. good performance relates to the way that animals perform a reaching movement. The adequacy of reaching movements was assessed using EWMN movement notation (Eshkol & Wachmann, 1958). This notational scheme describes the movement of distal end of each body segment relative to its proximal end. By notating all relevant body segments both the absolute and relative movement of each body part are scored (Whishaw & Pellis, 1990). EWMN has proved very useful in scoring the adequacy of movement of reaching in a number of animal models of neurological conditions, including stroke, Parkinson's disease, and Huntington's disease (Klein, Sacrey, Dunnett, Whishaw, & Nikkhah, 2011; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002; Whishaw, Pellis, Gorny, & Pellis, 1991). When EWMN was used to describe the performance of poor vs. good reachers, no differences in movement were obtained. That is, all animals performed the reaching movement in the same way despite variations in their endpoint performance. This finding definitively rules out the possibility that individual variation is in part attributable to some defect in the motor system analogous to what might occur in neurological conditions that are associated with changes in movement.

A fifth objective of the initial studies was to examine whether individual differences were related only to the skilled reaching performance of the rats or were a general feature of their test performance. Previous studies on the learning of skilled reaching for food in the single pellet task have shown that rats sequentially learn the task in three stages. These stages can be identified via three oppositions between a body part and the food pellet. The first opposition is a snout-pellet relationship in which the rat locomotes to the food location and sniffs the food. This opposition can be associated with any number of movements, but will always result in the rat locating the food. Then the rat learns that it can grasp the food, and this is the hand-pellet opposition, which organizes the transportation of the limb toward the food pellet for grasping. After grasping, the rat must learn that it can bring the food to the mouth, and this is the mouth- pellet opposition, which organizes the movements for withdrawing the limb to the mouth for releasing the food pellet into the mouth (Gharbawie & Whishaw, 2006). The analysis assessed the time required for each rat to progress through the three stages. The results indicated that although there was variation in the time taken by individual rats to progress from one opposition to another, the amount of time spent to learn these three oppositions were similar in the groups with good and poor reaching performance. This finding shows that skilled reaching movement is learned in a similar sequence and in a similar time frame by rats that subsequently display good and poor reaching skills. Thus, the individual differences found in skilled reaching in rats are not related to the difference in the way they organize their movements serially or temporally. Individual difference only began to emerge as the rats began to reach for food. Thus, individual differences in reaching performance appeared to be unrelated to the general way that animals acquired the task, nonreaching demands of the task, or motivation to obtain food.

A sixth objective of the first experiments was to determine whether there were any obvious differences in brain morphology of the rats that might be related to their skilled reaching performance. Some anatomical and neurobiological measures that have been found sensitive to brain injury include brain weight, cortical thickness, pyramidal tract size, motor cortex cell number and AChE density in the motor cortex (Jones, Chu, Grande, & Gregory, 1999; Kleim & Jones, 2008; Kolb, 2003; Schallert, Kozlowski, Humm, & Cocke, 1997). Gross anatomical examination can also reveal whether pre-existing brain abnormalities, such as tumors, strokes, or other brain anomalies are present. It was found that individual variation in skilled reaching was not related to gross abnormality in the motor system. No differences were found in brain size, cortical area, pyramidal tract size, or neurochemical measures in the motor cortex. Therefore, both the anatomical and behavioral measures revealed that the individual differences in performance were not related to obvious pre-existing brain abnormalities, tumors, or other brain anomalies.

A source of individual differences was identified in the way that the rats used gestures for reaching, however. Reaching consists of a sequence of four gestures, including advance, grasp, withdrawal, and release forming a normal reaching movement. Each gesture is separated by a brief pause and change in the movement direction and speed (Alaverdashvili, Foroud, Lim, & Whishaw, 2008). Although, one occurrence of each gesture is sufficient to form a single reach, each gesture can also be repeated several times in a successful reaching movement. For example, if a rat were to miss the food on the grasp gesture, it might repeat that gesture in an attempt to get the food. The gesture analysis showed that increased number of gestures was related to poor reaching performance. The animals with poor reaching skills displayed high number of gestures in their performance relative to the animals with good reaching skills.

The excessive gestures may affect performance in a number of ways. First, they may indicate that the rat has not positioned itself appropriately and so cannot target the food accurately, resulting in reposition of the body and further reach attempts. Second, increased gestures may interfering with successful reaching by increasing the chance that a poorly directed movement may result in the rat knocking the food pellet off the shelf and thus incurring a miss. Third, the increased number of gestures may indicate that the rat has adopted a reaching strategy that is different from that used by a rat that makes few gestures.

In keeping with the idea that gesture number may be related to strategy selection, individual differences displayed by rats in skilled reaching may relate to the way that they learn the task. In principal, there are two ways to solve the task (Boakes, 1977; Flagel, Akil, & Robinson, 2008; Robinson & Flagel, 2009). A rat could use a goal-oriented strategy (Balleine & O’Doherty, 2010; Dickinson, 1994; Dickinson, Balleine, Watt, Gonzalez, & Boakes, 1995) in which it learns the location of the food and directs its reaching movement to that location. Such a goal strategy would ensure that the reaching movement is accurate and may thus result in good performance because the location of the food pellet does not change. Furthermore, the location of the food can be confirmed on every trial by sniffing. On the other hand, a rat may learn to make a sequence of movements, which hopefully results in obtaining the food object. Such a habit strategy (Balleine & O'Doherty, 2010; Dickinson, 1994; Dickinson, Balleine, Watt, Gonzalez, & Boakes, 1995) would be reinforced by obtaining food on some reaches but may nevertheless result in poorer overall reaching success. Each misses would then result in another attempt and repeating attempts would then become a "feature" of an animal's performance. Thus, poor reachers might develop such a habit strategy as is supported by the gestural analysis that showed that poor reaching is characterized by many gestures.

In summary, the results from the first two experiments of the thesis indicate that reliable individual differences on skilled reaching performance of the rats exist. They are not related in an obvious way to the training procedures, amount of practice, or brain correlates that were examined. It is suggested that they may be due to the learning difference adopted by the animals. In order to investigate this variability more, we tried to change the brains by the effects of psychomotor stimulant drugs such as amphetamine and nicotine. The results will be discussed next.

Sensitization and skilled reaching

In the examination of the performance of rats in skilled reaching, it was found that there are considerable individual differences in the performance of the rats. The top half of each group of rats in terms of reaching success were designated as the good reach group and the bottom half were designated as the poor reach group. In the absence of any obvious cause of the variability in performance of the groups, it was proposed that the groups adopt different strategies in solving the problem of reaching with a hand for food. Rats that treat the food as an object at a location may excel because they direct their movements in relation to the food's location. Rats that merely acquire a sequence of movements that they execute in the general location of the food may do poorly because they rely on chance accuracy.

In independent investigations, it has been suggested that rats performing in food reward tasks can also be divided into two groups. Rats may focus their attention on the location of a food reward or they could arbitrarily attend to some irrelevant cue that they associate with the reward. Rats that display the former behavior have been termed “goal-trackers” and rats that display the latter behavior have been termed “sign-trackers”. It was hypothesized that the behavior of the GR and PR groups in the skilled reaching task may be analogous to the behavior of goal- and sign-trackers. If this were the case, then, using procedures that influence the incidence of goal- vs. sign-trackers may influence the incidence of GR and PR. This hypothesis was tested in two experiments.

The psychostimulant drugs are well-known chemicals because of their behavioral activating effects. Repeated exposure to the drugs such as amphetamine or nicotine leads to an enduring enhancement of the activating effects, which is called behavioral sensitization (Kalivas & Stewart, 1991; Robinson & Becker, 1986). Sensitization changes behavior (Feeney & Sutton, 1987; Goldstein, 2003; Maling & Acheson, 1946; Martinsson, Hardemark, & Wahlgren, 2003) and neuroplastic responses such as patterns of synaptic connectivity (Ramic et al., 2006; Robinson & Kolb, 1997; Stroemer, Kent, & Hulsebosch, 1998). These changes are developed gradually and lasted for months after the termination of drug treatment (Paulson, Camp, & Robinson, 1991).

Sensitization also influences the propensity of rats to become goal- or sign-trackers in subsequent behavioral tests (Flagel, Watson, Akil, & Robinson, 2008; Robinson & Flagel, 2009; Saunders & Robinson, 2010). Presumably, the synaptic capacity used up in the process of becoming sensitized renders the animals more likely to become sign-trackers than goal-trackers. If goal tracking vs. sign tracking are related to GR vs. PR strategies, then rats that are sensitized should be more likely to be PR than GR. Therefore, it was expected that behavioral sensitization induced by prior repeated administration of amphetamine or nicotine would influence the number of rats that become either GR or PR.

In the initial phase of the experiments, rats were treated with either amphetamine or nicotine in a sensitization paradigm. The sensitization procedure was successful in producing rats that met the criteria of sensitization, in that their response to a test dose of the drug after a sequence of daily drug administrations was enhanced.

It was found that the behavioral sensitization induced by prior repeated administration of either amphetamine or nicotine did not affect the acquisition and performance of single pellet reaching in sensitized animals. The acquisition and performance of skilled reaching were not different between sensitized and non-sensitized rats. Both drug groups (amphetamine and nicotine) reached similar amount of total success, single reach success and number of attempts relative to the saline groups during training and testing periods. But sensitization to amphetamine or nicotine has differential effects on animals with good or poor reaching skills. Comparing the animals with good and poor reaching skills in sensitized and non-sensitized groups showed that sensitization to amphetamine had different effects on subgroups that displayed good or poor reaching skills. There was an increase in successful reaches made by the sensitized-GRs. But no effect was found on the sensitized-PRs reaching performance relative to the non-sensitized poor reachers. Sensitization to nicotine had a detrimental effect on the way movements were made and decreased performance in rats with good reaching skills.

In summary then, sensitization with amphetamine and nicotine did influence subsequence performance. Following amphetamine sensitization, the GR in the sensitized group performed somewhat better than the GR in the control group. Following nicotine sensitization the success of the animals was not altered, although the movements used by the sensitized rats were poorer than those of the control group. The main results, however, did not suggest that sensitization altered individual differences in the predicted direction of producing more rats that could be classified as PR. Thus, the experiments do no lend support to the idea that it is differences in learning strategy that account for why rats turn out to be either good or poor reachers. It seems more likely, then, that there must be some structural basis for the rats' performance. It is likely that a structural difference resides in the motor cortex. In order to test this idea, a final experiment was conducted.

Motor cortex and individual differences in skilled reaching

Given that the sensitization study, described above, did not provide evidence that there was a change in the biases of the rats that would increase the number of PR, the studies prediction, a different hypothesis was tested. The question asked was whether some aspect of the motor cortex was involved in generating individual differences in skilled reaching. In order to investigate the role of the motor cortex in the reaching variability, a lesion study was conducted. Small lesions were made in motor cortex contralateral to the preferred forelimb. The rats were well trained and divided into GR and PR groups prior to receiving the lesions. The expectation was that there should be a decrease in successes in animals with good reaching skills. That is, in order to be a GR, the expectation was that an intact and highly functioning motor cortex is required.

This method of using motor cortex lesions to investigate skilled motor behavior is one of the most common and classic ways to study brain-behavior relationships. In the earliest investigation, Peterson and Francarol (1951) found the relationship between handedness and the motor cortex. By making lesions in the motor cortex of pretrained rats, they found a shift in limb use. Many studies have subsequently replicated this finding by using different kinds of motor cortex lesions. For investigating the role of motor cortex in the individual differences in skilled reaching, several factors should be considered. The lesion would have to be consistent in all animals. The devascularization of surface blood vessels (pial strip) model was chosen because this model provides well defined and consistent infracts. The lesion would also have to be small. A small lesion would maximize performance and also would not mask the variability in the behavioral outcome due to the severity of the impairments. Finally, the lesion should be in the caudal region of the forelimb because this are is likely most closely associated with control of the forelimb (Gharbawie, Karl, & Whishaw, 2007; Friel et al., 2005). In the present study, consistent lesions that were small in size were successfully produced in the caudal region of the forelimb motor cortex in all of the rats.

The results showed that the behavioral deficits were mild, featuring a decrease total success, single reach success and an increase in the number of attempts during the early post-lesion period. Previous studies have shown that after a "standard" motor cortex lesion, severe behavioral deficits do occur (Alaverdashvili, Moon, Beckman, Virag, & Whishaw, 2008; Erickson, Gharbawie, & Whishaw, 2007; Gonzalez & Kolb, 2003; Gonzalez et al., 2004; Hsu & Jones, 2005; Metz, Antonow-Schlorke, & Witte, 2005; Whishaw, 2000; Whishaw, Pellis, Gorny, & Pellis, 1991) but severe deficits were not produced in the present study. Thus, the intention of producing a small lesion that still had mild deficits on performance was achieved.

The central result of the study was that despite similar sized lesion of the motor cortex in the rats designated as GR and PR, a mild reaching deficit observed only in the performance of the GR. Rats with good reaching skills displayed a decrease in successful reaching (both total success and single reach success). The deficit in single reach success did not improve with three weeks of rehabilitation. In addition, there was an increase in the number of attempts only in the GR group. Thus, the main effect of the lesion was to decrease successful reaching in the GR group and to leave the PR group unaffected. This finding seemingly confirms the prediction underlying the hypothesis that was tested by the experiment and suggests that the substrate that mediates the differences between GR and PR is the motor cortex.

There is one caveat to the conclusion that the substrate of the difference between GR and PR is the motor cortex. The elemental analysis of the rats reaching performance showed that both PR and GR displayed a chronic decrease in movement performance. Thus, the motor impairment produced by the lesion may have led to the decrease in the performance of the GR group. At the present time, the relationship between movement elements and endpoint measures is not certain. Clearly after most lesions to the motor system, the two measures undergo correlated changes. After a recovery period, however, endpoint measures do undergo improvement, and are likely mediated by compensatory movements, which is not matched by improvements in movement.

On the basis of information at hand, however, it is possible to speculate that in fact the lesions were successful in identifying the motor cortex as the substrate for performance and therefore the substrate for individual differences. It is not likely, however, that frank structural damage is the variable related to individual differences in performance. There could be differences in many features of motor cortex, including synaptic connections, neuronal morphology, or growth factor and other chemical content. It is interesting in this respect that Kleim et al. (2006, 2010) have found that the content of BDNF in the motor cortex of the human brain is related to the size of the forelimb representation of motor cortex. Future studies could investigate whether BDNF content or other changes in motor cortex are related to the skill with which an animal is able to use its hands for reaching for food.

4. Conclusion

In conclusion, this study investigated individual differences in skilled reaching performance in rats. It was thought that identification of skilled reaching would reveal something of the control process of skilled reaching, provide insights into the evolution of skilled reaching, and would be relevant to the performance of animals used in studies that investigate neurological studies. Five experiments were performed and these investigated the profile of individual differences in normal rats and also manipulated the neuronal condition of rats in order to reveal neural substrates for individual differences.

Skilled difference in endpoint measures of reaching success was found to be a robust feature of the performance of the rats. The differences were constant in the face of the extent of training given to the animals, manipulations of the training conditions, and the trial-by-trial performance of the animals. Individual differences were not related to the way that rats acquired the task, their motivation to perform the task, or to the gross differences in the anatomy of their motor system.

It was hypothesized that individual differences may be related to the strategies that rats adopt to perform skilled reaching, with GR solving the task using a goal strategy and PR solving the task using a habit strategy. This idea was tested first by sensitizing rats with the stimulant drugs amphetamine and nicotine, and then training them on the skilled reaching task. The prediction was that sensitization would increase the probability of the use of a habit strategy and so increase the probability that a rat would be a PR. The predication was not born out and the sensitized rats displayed no differences in their performance profile relative to the control rats.

A final experiment tested the idea that substrate for performance and individual differences is the motor cortex. Well-trained rats divided into groups of GR and PR were given small motor cortex lesions with the prediction that disruption of the motor cortex would preferentially disrupt the performance of GR. The prediction was born out as the lesions had little effect on the endpoint measures of the PR but they did reduce successful reaching of the GR. The suggestion is made that future studies could investigate the structural and neural chemical organization of the motor cortex with the aim of revealing the neural substrate of individual differences.

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Appendix 1

Edited video clips display animals' performance in the single pellet-reaching task demonstrating good and poor reaching skills. The first video clip shows a successful reach on the first reaching attempt performed by a good reacher. This video clip is played twice, first time in normal speed (100%) and the second time in a slower mode (40%). The second video clip shows unsuccessful reaching attempts performed by a poor reacher. This video clip also is played twice, first in normal speed and then in a slower pace.

Appendix 2

Edited video clip shows an animal performing tapping attempts. This video clip demonstrates a successful reach on tapping attempts. These attempts are performed outside of the reaching box without a new aiming movement. This video clip is played twice, first in normal speed (100%) and then in a slower mode (40%).