**SOUND-INDUCED BEHAVIOURAL ACTIVATION IN THE NORMAL
AND HALOPERIDOL-TREATED RAT**

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DEDICATION

This work is dedicated to, Dad, who always takes the time to listen and mentor, encourage and teach. Thank-you for supporting my passion for writing and for taking me ice fishing. Thank-you for teaching Liz and I that we should reach for the big leagues. This work is dedicated to Liz, who is the truest friend one could have. I believe in you, and I know that we are both going to have many amazing adventures on our travels. This work is dedicated to Mom, who has a way of making the everyday special. Thank-you for teaching me to treat everyone with respect and compassion. This work is dedicated to Lori. Your future is bright and you are going to go far. I am honored to have had you as my officemate and Lethbridge mate. This work is dedicated to Donald, who asks the best questions and has the best stories. This work is dedicated to Grandma Clark, whose inner strength and faith inspire me. Thank-you for your daily prayers and for our Friday night dinners together. This work is dedicated to Grandma Stauffer, whose grace and friendship have helped me to grow roots and wings. This work is dedicated to Christina Vasili, whose energy and late night get-togethers inspire me to dream big. I believe in you, and I want to thank you for always going the extra mile for me and for others. This work is dedicated to Essam. I love you, and I know that my life has changed because of your strength, faith, humor, and kindness.

ABSTRACT

Diseases of the central and peripheral nervous systems affect one in five people in North America. Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's disease, and occurs in approximately 1% of the general North American population. PD is a progressive movement disorder that is characterized by resting tremor, rigidity, bradykinesia (slowness of movement) or akinesia (absence of spontaneous movement), as well as postural instability. Current treatment of PD is symptom-based, and no pharmacological treatment currently exists to slow the progression of bradykinesia and akinesia. In fact, pharmacological therapies produce motor side effects in advanced stages of the disease. Given the difficulty in initiating and controlling movement as PD advances, and the ineffectiveness of medical therapies after prolonged treatment, physical and music therapies can be used to supplement classical therapies. Listening to, and performing, music affects a number of neural regions, including those that mediate motor behaviour, arousal or activation, and emotion. Despite anatomical connections between the auditory and motor systems at the level of the spinal cord, brain stem, midbrain, and cortex, the neural and behavioural mechanisms for sound-induced activation remains unclear. It is known, however, that PD patients recruit external sensory stimuli to improve movement. The aim of the current research was to create an animal model of sound-induced activation and to test the effect of previous motoric experience on the potency of auditory stimuli. To investigate behavioural activation in the normal and haloperidol-treated rat, two tasks were used: 1) orienting responses were analyzed for movement components in saline and haloperidol treated rats

to find out if rats responded in the same to a variety of naturally produced and generated activating sounds, and 2) a grid climbing task allowed for the righting components of naïve and familiar cataleptic rats to be compared. Our findings revealed that familiar auditory cues could release parkinsonian rats from catalepsy. The current research supports the theory that auditory stimulation retains "special access" to motor regions otherwise impaired in PD and likely bypasses basal ganglia circuitry to normalize movement through alternative pathways.

ACKNOWLEDGEMENTS

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CHAPTER ONE

INTRODUCTION

INTRODUCTION

This thesis will present experiments conducted on sound-induced behavioural activation in a rat model of akinesia in Parkinson's disease (PD). In three sections, this introduction will review the literature on PD, the literature on behavioural activation, and the literature on the use of sensory cueing and music in the treatment of PD symptoms.

Parkinson's disease

The discovery of Pakinson's disease as a unique clinical condition and the recognition of nigral dopamine as a central feature of the disease shape our current understanding. British physician James Parkinson first described PD as a distinct disease almost 200 years ago, in 1817 in "An Essay on the Shaking Palsy." Parkinson published six case studies of men in his community who exhibited a worsening of motor abnormalities in gait and posture over a number of years. In his pivotal essay on paralysis agitans, the shaking palsy, Parkinson was the first to note three cardinal symptoms of the disease (excluding rigidity) and comment on its progressive nature (1817, p.225):

> As the disease proceeds towards its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent. The patients walks now with great difficulty, and unable any longer to support himself with his stick, he does not venture on this exercise, unless assisted by an attendant, who walking backwards before him, prevents his falling forwards, by the pressure of his hands against the fore part of his shoulders.

Further, Parkinson hypothesized that the basis of the disease resulted from damage to the medulla, but was unable to test this idea in his lifetime. One decade following the publication of Parkinson's essay, physician J.-M. Charcot (1877) met with patients who he diagnosed with Parkinson's disease, and wrote on the unilateral and progressive nature of PD. Although it was noted in the late nineteenth century that melanin-containing cells of the SNc are reduced in PD (Fig 1.1), it was not until 50 years later that researchers were able to connect PD symptoms with the death of these dopamine (DA) neurons in the SNc that provide dopaminergic (DAergic) innervation of the striatum. The following discoveries made this connection possible: 1) Rosegay (1944) published the first clear demonstration of a pathway from the SNc to the striatum; 2) Carlsson (1959) showed that dopamine functions as a neurotransmitter; 3) Hornykiewicz (1963) showed that dopamine concentrations are decreased in the striatum of PD patients, particularly in the side of the brain contralateral to symptom onset.
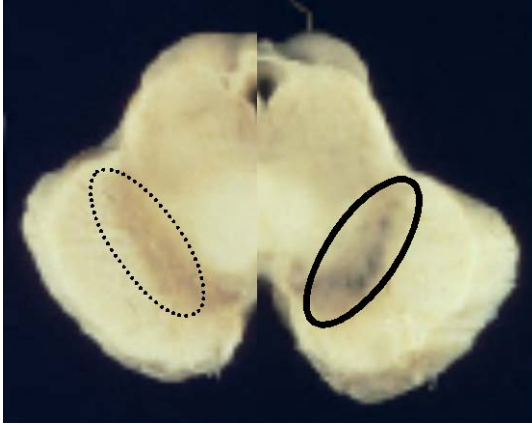
Fig. 1.1. Dopaminergic cell death in the substantia nigra pars compacta. Right: Intact substantia nigra containing a high amount of melanin containing cells. Left: Loss of DAergic cells in parkinsonism. Modified from http://faculty.washington.edu/alexbert/MEDEX/Fall/pdnigra.jpg.

Recently, studies show there are sensorimotor abnormalities, and thus the conception of PD as a strictly motor disorder is incomplete (Abruzzese and Berardelli, 2002; Marsden, 1982; Morris et al., 1994b). Non-motor symptoms that increase with disease severity include depression, cognitive decline, pain, and sleep (Friedman and Friedman, 1993; Koller, 1984; Norman et al., 2002; Quinn and Marsden, 1986). A diagnosis of PD is based on clinical observation of a neurologist and can only be confirmed through post-mortem autopsy. A clinical diagnosis can also be supported by the unilateral appearance of symptoms, a positive response to treatment with levodopa, and the absence of another movement disorder that might lead to signs of PD (Ebadi and Pfeiffer, 2004).

Model of basal ganglia function

The cardinal symptoms of PD have been associated with abnormal intrinsic basal ganglia (BG) activity that leads to decreased activation and control of motor cortex (Ridding, Inzelberg, and Rothwell, 1995; Watts and Mandir, 1992). The BG are subcortical nuclei that provide background tonic activity for motor cortex (Ebadi and Pfeiffer, 2004) and through dopamine-glutamate interactions, increase the signal-to-noise ratio of corticothalamic activity (Horvitz, 2002; Rebec, 2006). The BG consist of three nuclei, including the striatum (composed of the caudate body and putamen) and the globus pallidus and comprise the major nuclei of the extra-pyramidal motor system. The primary input structure to the striatum is the substantia nigra pars compacta (SNc). The output structures of the BG are the internal capsule of the globus pallidus and the substantia nigra pars reticulata (SNr). The current understanding of BG function

emphasizes two functional pathways that are known as the "indirect pathway" and the "direct pathway" (Albin, Young, and Penney, 1989; DeLong, 1990). Normally, DA provides a net excitatory input to thalamocortical projections and controls movement force, movement initiation, and planning based on motor set through disinhibition of the thalamus (Fig. 1.2) (Ebadi and Pfeiffer, 2004; Tecuapetla et al., 2007). The direct and indirect pathways for movement allow for permissive and restrictive motor signals, respectively.
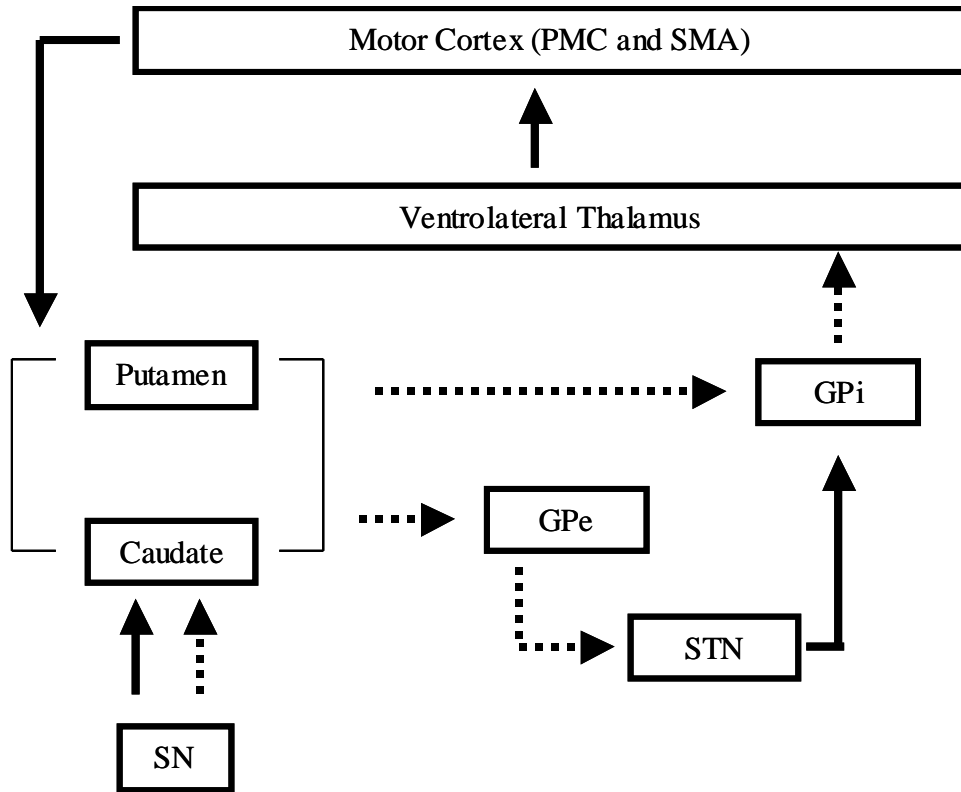
Fig 1.2. Intrinsic connections in the normal basal ganglia [adapted from Albin, Young, and Penney (1989) and DeLong (1990)]. Solid lines indicate excitatory (Glutamatergic) input, and inhibitory (GABAergic) input is indicated by dashed lines. The direct pathway travels from the caudate-putamen (striatum) to the internal globus pallidus (GPi), and serves to decrease inhibition of the ventrolateral nucleus of the thalamus (VL thalamus). The indirect pathway proceeds from the striatum to the external globus pallidus (GPe), which then excites the GPi via the subthalamic nucleus (STN).

In PD, reduced dopaminergic influx to the striatum produces a net increase in inhibition, leading to decreased excitation of motor cortex by the VL thalamus and resultant hypokinesia (Fig. 1.3).
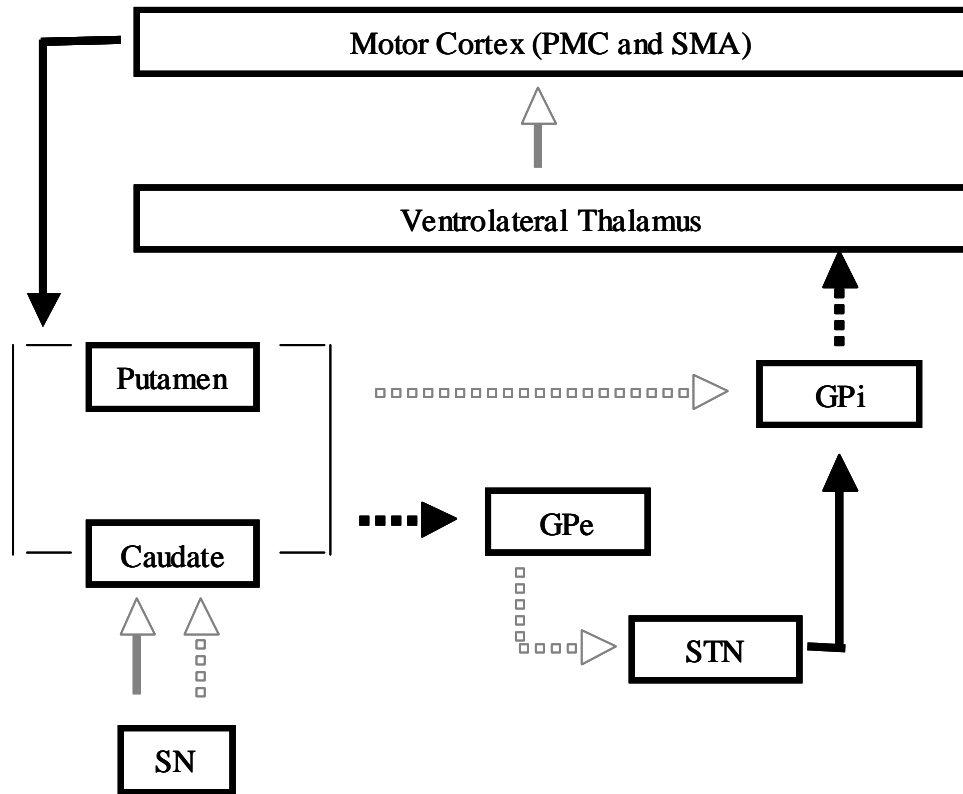
Fig 1.3. Parkinsonian basal ganglia function (adapted from Burch and Sheerin, 2005). Reduced dopaminergic innervation from the SNc decreases activation of motor cortex by the VL thalamus. The white arrows with grey outlines indicate a decreased impulse, and the black arrows indicate an increased impulse. There is increased inhibition of the VL thalamus along the direct path, leading to reduced excitatory output. Along the indirect pathway, there is a failure to inhibit the ST, leading to increased inhibition of the thalamus by the GPi and a subsequent poverty of movement.

The BG is involved in the production of motor behaviour. Evidence also highlights a role in sensorimotor integration, selection of a single motor program, tonic background activity for ongoing locomotion, control of movement force, inhibition of competing motor programs (Escola et al., 2002). In addition to the direct/indirect BG model of motor dysfunction, PD is related to fronto-striatal executive deficits that typically worsen with disease progression (Owen et al., 1992; Rowe et al., 2008).

A closer look at PD patients within the laboratory and the real world suggest that the motor symptoms of bradykinesia (slowness of movement) and akinesia (absence of spontaneous movement) have a sensory component (Bazyan, Getsova, and Orlova, 2000; McDowell and Harris, 1997; Sacrey, Clark, and Whishaw, unpublished). In PD, external cues can have a disproportionately large effect on movement initiation and execution (Almeida, Wishart, and Lee, 2002; McDowell and Harris, 1997), and internally guided movements become particularly difficult (Jahanshahi et al., 1995). The influence of external stimuli on the maintenance of behavioural arousal relates to attention, and altered DA transmission is known to produce attention deficits during continuous performance tasks in neuroleptic-treated human subjects and animal subjects (Fowler, 1999). A dose-dependent decrease in responding to incentive stimuli has been documented following treatment with DA antagonists (Beninger, 1982). Additionally, cells of the SN show increased activity following conditioned and non-conditioned sensory events (Horvitz et al., 1997) and display altered responses to sensory stimuli in animal models of PD (Schneider, 1991), providing a putative mechanism for behaviours left intact in PD. Reduced evoked somatosensory potentials observed in PD and Huntington's disease are believed to result from deficient sensory integration by the BG

and contribute to deficits in postural control and other motor deficits (Boecker et al., 1999; Cham et al., 2007). When parkinsonian akinesia is experimentally produced in animals, the subjects become less responsive to sensory stimuli that would normally activate behaviour (Teitelbaum, Schallert, and Whishaw, 1983).

Pathways for voluntary movement

There are at least two pathways to motor cortex from basal ganglia for voluntary movement. In healthy subjects, the basal ganglia send excitatory innervation to the SMA via the ventrolateral nucleus of the thalamus. The SMA then sends projections to primary motor cortex via the PMA. An alternative pathway, hypothesized to mediate compensation in PD, extends from the BG to the cerebellum to the PMA, thus bypassing the SMA when external cues are given. Using TMS, Cunnington et al (1995) revealed that patients, in contrast to healthy controls, use SMA only during internally driven movements and during both cued and non-cued conditions during sequential movements. It is evident from the above electrophysiological and behavioural studies that sensory systems are changed in PD patients, thus providing a possible therapeutic avenue.

Neurophysiological changes

In addition to changes in BG and motor cortex, changes in additional brain regions also contribute to PD symptomology. PD is a progressive neurodegenerative disease associated with the loss of dopaminergic neurons of the substantia nigra pars compacta (SNc), the presence of cytoplasmic inclusions known as Lewy bodies, and changes in virtually every neurochemical system of the central nervous system

(Bernheimer, Birkmayer, and Hornykiewicz, 1961; Hughes et al., 2001). Because basal ganglia output through GPi and SNr is disrupted, cortical regions responsible for movement, including the SMA and PMA, exhibit a decrease of normal activity and an increase in synchronicity (Ridding, Inzelberg, and Rothwell, 1995). In particular, SMA, a region known to mediate internally generated movement, loses its primary source of excitatory input, whereas the PMA mediates externally driven movements (Cunnington et al., 2001; Taniwaki et al., 2003). Altered motor cortex processing and reduced recruitment of spinal motor units are associated with altered gait and signal detection performance in which PD patients become disproportionately sensitive to external cues to guide their movements as proprioceptive deficits lead to impairment and akinesia (Caviness et al., 2000; Escola et al., 2002; McDowell and Harris, 1997).

Epidemiology and causes

When considering incidence and prevalence rates for PD, it is important to note that epidemiological studies are based on clinical diagnoses and thus can, and do, vary between regions (Ebadi and Pfeiffer, 2004). PD does not have a known cause, but a number of environmental and genetic factors appear to play a role. Thus, the majority of PD cases are referred to as "idiopathic," or being without a known cause. Age is the strongest predictor of PD and is rarely diagnosed in people under the age of 50 years old. In addition to age, risk factors include living in a rural environment, closed head injury, family history (some cases of early-onset familial PD have been associated with mutation in the Parkin gene), and exposure to industrial chemicals or pesticides (Quinn, Critchley, and Marsden, 1987; Olanow and Tatton, 1999). Exposure to compounds that inhibit DA

cells, including MPTP and neuroleptics, produce parkinsonism in patients and animals. Animals showing neuroleptic-induced catalepsy can be reversed by electrical stimulation of sites used therapeutically in human patients (Degos et al., 2005). A loss of 80-90% of the DAergic cells of the SNc (Fig. 1.1) produce signs of parkinsonism, and although the ultimate cause of this cell death is not yet known, PD is linked to dysfunction of mitochondrial complex 1 through exposure to environmental toxins or chemicals (Gu et al., 1998; Schapira, Cooper, Dexter, Clark, Jenner, and Marsden, 2008). A number of hypotheses (e.g., excitotoxicity, rotenone exposure, oxidative stress, exposure to heavy metals) support this essential mechanism in the cellular death observed in PD (Ebadi and Pfeiffer, 2004; Schapira et al., 1990).

Treatment

Although a comprehensive review of medications for PD is beyond the aim of this thesis, a brief review of medical and complementary treatment strategies for PD is relevant. PD treatment is symptomatic and is not able to slow or prevent the progression of the underlying neuropathology (Marsden and Parkes, 1977; Zetusky, Jankovic, and Pirozzolo, 2004). Pharmacological management consists of the administration of levodopa (L-dopa), dopamine agonists, cholinergic blockers, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors for patients (Ebadi and Pfeiffer, 2004). Early in PD, motor symptoms typically present unilaterally and consist of tremor or rigidity (increased resistance to passive movement) (Zetusky, Jankovic, and Pirozzolo, 2004). Non-motor symptoms can also be present and include olfactory deficits (which are often the first to appear), sleep disturbances,

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emotional changes, and dementia. PD patients experience balance-related changes in motor control, and report a high incidence of PD-related falls every year (Koller et al., 1989). In advanced PD, akinesia, falls, and postural disturbances affect quality of life and can become resistant to pharmacological intervention (Zetusky, Jankovic, and Pirozzolo, 2004).

Unfortunately, balance deficits are largely unaffected by dopamine agonists and cholinergic blockers (Bloem et al., 2004). Bradykinesia (slowness of movement) is associated with disability as the disease progresses, as postural instability also becomes evident. After patients are treated with L-dopa/carbidopa or dopamine agonists for a number of years, the following complications often occur: 1) wearing off effects; 2) on/off effects; and 3) dyskinesia (Barbeau, 1969; Marsden and Parkes, 1977). Akinesia progresses in the advanced stages of PD, as slowness of movement can advance to absence of movement (Ebadi and Pfeiffer, 2004). Patients with symptoms resistant to pharmacologic treatment may undergo surgical treatment (e.g., subthalamic or pallidal deep brain stimulation), which has been shown to reduce medication requirements (Moro et al., 1999). Complementary therapies can also be used in conjunction with medication (Mak and Hui-Chan, 2004). Non-pharmacological therapies for PD include physical therapy, music therapy, and speech therapy. Thus, treatments that assist patients in adapting to their changing symptoms and medication programs become important for activities of daily living (Ebadi and Pfeiffer, 2005).

Behavioural Activation

Normal locomotion for example consists of numerous motor programs and sensory feedback systems functioning to produce movement. Teitelbaum, Schallert, and Whishaw (1983) review spontaneity in behaviour and the internal and external stimuli that can elicit such behaviour. Distinct neural systems, such as the allied reflexes responsible for postural control (e.g., Sherrington, 1896-1897; Sherrington, 1906), can be independently activated using environmental stimuli (Teitelbaum, Schallert, and Whishaw, 1983). PD, a disorder of movement 'organization,' 'activation,' or 'rhythm' (Sacks, 1973) creates a movement disorder in which the normal pathway for regulating movement timing, force, and initiation (BG) is deregulated due to a loss of DAergic innervation. Rats with damage to the hypothalamus and striatum also exhibit a decrease in spontaneous behaviour (Teitelbaum, Schallert, Whishaw, 1983). Acute administration of dopamine antagonists (e.g., haloperidol) in the rat produces a behavioural condition in which sources of activation are ineffective (DeRyck and Teitelbaum, 1983); haloperidol catalepsy is reflected in altered motor cortex activity and spinal motor unit recruitment (Burkhardt et al., 2007). Only those reflexes responsible for preserving static stance are left intact. For example, a rat exhibiting haloperidol-induced catalepsy will cling vertically to a grid for an extended duration of time unless presented with a sensory stimulus (e.g., tail pinch or neck bandage; De Ryck, Schallert, and Teitelbaum, 1980; Teitelbaum, Schallert, and Whishaw, 1983; Teitelbaum et al., 1976). Destabilizing the animal can also activate intact postural reflexes (Field, Whishaw, and Pellis, 2000; Teitelbaum, Schallert, and Whishaw, 1983). Thus, catalepsy is a model of PD akinesia in

which the environment of a subject can be manipulated to activate isolated reflexes (Bazyan et al., 2000; Whishaw, 1989).

Evolutionary Perspectives on Music

Before further discussion of auditory cueing in PD, a discussion of how music is processed in the central nervous system will be useful. Music is a specific environmental stimulus that is virtually ubiquitous in human society and is known to affect a wide range of biological, psychological, and physiological functions of the body (Merker 1999-2000; Povel and Essens, 1985; Thaut et al., 1999). Rhythm is the primary organizing unit of music and emerges as sound elements are grouped together. The profound effect of music on human behaviour has provided a rich source of study for philosophers, musicians, and most recently scientists: "Why do we listen to music?" and "How does it move us?" Currently, there are two theories regarding the emergence of music in human society: 1) the "auditory cheesecake" metaphor in which music has evolved as a byproduct of language, but serves no other psychophysical function beyond pleasure (popularized by Stephen Pinker) or; 2) sexual selection theory in which music and dance (which have been inseparable for most of human history) signal reproductive fitness to potential mates (it is typically the male in a species who performs and the female who elicits the song , a theory originally proposed by Darwin) (Levitin, 2006).

Processing of musical stimuli in the brain

The study of music as a biological function has become a rich field of study in the last decade. The auditory system has evolved to accomplish species- and environment-

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specific tasks and is comprised of cortical and subcortical nuclei adapted for feature extraction, anticipation, and production of the auditory gestalt (Musacchia et al., 2007; Repp, 2002; Repp, 2003; Repp and Keller, 2004). In fact, frequency resolution tuning curves of primary auditory cortex correspond to their psychophysical equivalent (i.e., biologically meaningful unit of sound) (Ehret and Schreiner, 1997). In musicians and non-musicians alike, engaging in music involves brain areas responsible for audition, language, attention and reward, memory, planning, and anticipation (Blood and Zatorre, 2001; Musaccia et al., 2007). There is a clear lateralization of language and music, with the right hemisphere generally assigned the function of music processing, and the left hemisphere known to play a special role in language perception and production (Sperry, 1961). Recent modern imaging studies highlight the preferential processing of rhythm in the left hemisphere, and prosodic features of speech and music located in the right (Limb et al., 2006). Further, vocal training or extensive experience with playing a musical instrument is known to change the way in which the brain engages in music, such that some functions become left lateralized (Limb, 2006). The considerable overlap between music and language processing across the two hemispheres is also important to note, as well as the components and skills needed for each module (Platel et al., 1997). Case studies and modern brain imaging have provided detailed insight into the neural regions responsible for a number of music-related behaviours. For example, there are multiple reports of aphasia without amusia, highlighting the modularity of the musical and linguistic auditory systems. Within musical stimuli, modern brain imaging has revealed the shared and divergent substrates responsible for processing musical rhythm, syntax, pitch, timbre, and semantics (Limb, 2006). For example, Zatorre (2001) used PET to

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determine which areas of the brain were most active while subjects listened to a burst of sound or a melody, and revealed that divergent areas are involved in processing different elements of musical pitch. Heschl's gyrus in primary auditory cortex was activated when listening to a burst of noise, whereas listening to melodies involved frontal cortical areas. Finally, music has a potent effect on arousal and attention correlates during various music tasks. Different patterns of activation for pleasant and unpleasant musical stimuli can be found using functional Magnetic Resonance Imaging (Koelsch et al., 2005).

Auditory-motor connectivity

There is a rich literature highlighting auditory-motor connections throughout the central nervous system (Galazyuk and Volkov, 1994; Paltsev and Elner, 1967; Rossignol and Jones, 1976). Because PD is associated with central processing deficits in timing, therapies that improve the timing of motor acts can be useful for patients (Sacks, 1973). Timing is a distributed function in the brain, and underlying mechanisms can be traced to cortical, midbrain, cerebellar, and spinal networks (Molinari et al., 2003). The role of previous social and motor experience in responding to musical or auditory stimuli is clear, and familiarity with musical pieces and discrete auditory cues can have an effect on non-musical behaviour and physiology (Wöhr, Houx, and Schwarting, 2008). Psychophysical studies suggest subliminal and supraliminal coupling mechanisms underlying motor entrainment and response to auditory stimuli (Thaut, 2005).

Auditory startle versus cued movement

The description of movement following auditory stimuli necessitates a brief discussion of mechanisms responsible for an acoustic startle response to a brief loud sound compared to the pathways involved in a more complex body orienting and righting response following a sound cue. A monosynaptic pathway is known to underlie auditory startle characterized by brief contraction of craniofacial and skeletomotor muscles (Thompson, 2005). Cochlear root neurons project to the ventral pontine reticular formation, which then integrates at a premotor level and sends descending projections to the spinal cord and facial motor nucleus for a brief motor response (Thompson, 2005). Conversely, a righting response that is elicited following key jingle is likely mediated by centers above the level of the reticular formation and is reliant on the integration of visual, somatosensory, proprioceptive, and vestibular inputs. It is known that natural sound stimuli activate neural regions that receive both proprioceptive and auditory afferents at cortical levels (Alexeenko and Verderevskaya, 1976). We hypothesize that sound-induced orienting within an open field, and the inferior colliculus, thalamus, auditory association areas, and parietal areas are involved in the righting movements made during a grid-climbing task.

Music therapy

The use of music in therapy has shifted from a strictly socio-emotional application to one of neurological improvement, thus propelling music researchers into the area of neuroscience and movement research. Paltsev and Elner (1967) first showed the sensitivity of the cortical, subcortical, and spinal areas of the motor system to auditory

stimuli. There is convergent evidence that regulation of behaviour requires areas beyond classical sensory areas (Radionova and Shmigidina, 1973). There is evidence for immediate synchronization to auditory rhythm during intrinsically rhythmic motor behaviours such as finger tapping and steady state gait in laboratory studies (del Olmo et al., 2006; Thaut et al., 1996). Further, self-paced tapping and sequential movements of the digits involve the premotor cortex, primary motor cortex, supplementary motor area (SMA), and contralateral cerebellum, areas that are changed in PD during movement (Moritz et al., 2000). Neural mechanisms involved in motor entrainment to auditory rhythm in PD could include: 1) reticulospinal pathways to phase-lock motor neurons and increase motor unit excitability prior to movement (Thaut et al., 1999; Rossignol et al., 1976); 2) projections from auditory cortex to basal ganglia which could help compensate for deficient BG activation (Otellin, 1970); 3) activation of premotor area via the cerebellum, bypassing deficient inputs to SMA (Cunnington et al., 2005); 4) activation of the pedunculopontine nucleus and descending motor pathway (Muthusamy et al., 2007; Pahapill and Lozano, 2000); or 5) involvement of the posterior hypothalamus (Jackson et al., 2008). Current theories of music-induced therapeutic benefits for movement disorders emphasize pulse-salient models; intrinsically rhythmic networks synchronize to external felt pulse patterns shaped by anticipation, producing coupled oscillation (Thaut, 2005). That is, variability in movement timing can be improved using external auditory inputs that can be consciously and unconsciously matched (Thaut et al., 1999).

Retrieval of motor programs

Motor behaviour can be entrained or primed immediately to auditory cues through coupled oscillator synchronization or through training effects over time (Ma et al., 2004; Lewis, Byblow, and Walt, 2000; Thaut et al., 1996). These numerous connections between auditory and motor systems allow music to entrain a number of motor behaviours by assisting during learning or the retrieval of learned motor programs. By providing polyphonic and temporal information, music can retrieve motor memories and give sequence to movements (Ma et al., 2003). Sacks (2007) observed that music could be used to prompt recall of learned and well-practiced movements such as walking in patients who were unable to recall how to walk, despite no physical causes. Sacks' own experience provides a striking example. He had been given a recording of Mendelssohn's Violin Concerto in E minor, following a climbing accident in which he tore the quadriceps of his left leg. When putting weight on his leg for the first time, he observed that he had seemingly "forgotten" how to walk; the automatic nature of walking had left him. On one occasion, however, he reports that Mendelssohn's concerto began playing vividly in his mind, and he "suddenly remembered how to walk." Sacks reports similar cases in patients following hip and bone repair surgeries where the imagining of music has acted as a cue for motor memory and has reinstated walking.

Sensory cueing in Parkinson's disease

External sensory mechanisms are used to normalize movement in PD patients (Morris et al., 1994b). As mentioned, humans and nonhuman animals can be activated or aroused using external stimulation or by altering brain regions responsible for the

ongoing arousal state of the animal. Martin (1967) and Sacks (1973) first documented the potent organizing and initiating effect that sensory (i.e., auditory and visual) cues can have on movement deficits in parkinsonism. Patients who present with freezing often do so in the presence of distracting visual cues such as doorways or other objects that disrupt optical flow (Almeida, Wishart, and Lee, 2002). Providing a patient with horizontal lines or a laser point on the floor, for example, can release patients from freezing and provide an external template to organize movements to. Auditory cues, such as musical pieces with an embedded rhythmic cue on each heavy beat, can improve spatiotemporal parameters of gait in PD patients and reaching movements in stroke patients (Thaut et al., 1999). Martin (1967) was the first to demonstrate that particular visual cues (such as high contrast lines perpendicular to the patient, with a distance slightly greater than their average stride length (Sidaway, 2006; McIntosh et al., 1997; Thaut et al., 1996) could aid locomotion. Sacks (1972) worked with post-encephalitic patients who were severely cataleptic or "frozen" and discovered that salient musical and visual cues could temporarily release patients from periods of akinesia, particularly those patients who had been musical prior to their disease. Currently, the literature on visual and auditory cueing in PD focuses on speed, stride length, symmetry, velocity, and range of motion during gait (Sidaway et al., 2006; Morris, 1994a). Experience with an auditory cue has been shown to slow an increase in disability in patients when the sound stimulus is used in conjunction with a physical therapy program, as compared to non-cued age- and disease-matched controls (Marchese et al., 2001). Interestingly, Chuma et al (2005) found that PD patients were able to reproduce a repetitive thumb movement after training with an auditory cue, and demonstrated that cued movements in PD may be mediated by

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cerebellar connections with the premotor cortex, bypassing the SMA (Cunnington et al., 1995). Music therapy has been recognized as a distinct discipline since the 1950's, and now plays an increasingly central role in the management of symptoms associated with disorders of movement, thought, and development. Music therapy, and specifically neurologic music therapy (NMT), applies music to PD symptoms within the guidance of neuroscience research. To summarize, auditory PD is associated with compensatory changes in responding to environmental stimuli, and music therapy is now an allied health discipline that applies neuroscience research based programs (Ebadi and Pfeiffer, 2004).

Unanswered Questions

The organization of motor behaviour is influenced by the activity of striato-thalamic-cortical loops (Berardelli et al., 2001; Parr-Brownlie and Hyland, 2005). Human patients and animal subjects with parkinsonian movement disorders show reduced movement organization, force, and speed (De Ryck et al., 1980; Miklyaeva, Martens, and Whishaw, 1995). In many animal species, sound stimuli convey environmental and conspecific information, and it is well known that sound has physiologic and arousal effects on behaviour (Sadananda, Wöhr, and Schwarting, 2008). It is likely that sound has access to motor areas that would otherwise be left inaccessible in the parkinsonian brain (Brudzynski and Pniak, 2002). The basis of sound-induced movement can be investigated in the rat, a species extensively used in PD and behavioural activation research.

Despite the rich literature on music and the brain, the underlying mechanism for music-induced movement remains unclear, and an animal model of music-induced

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benefits in PD has not been developed. Specifically, it is not known if sound induces activation through "classical" auditory-motor connections responsible for defensive or orienting behaviour, or if the effect depends on a neural module dedicated to behavioural activation. The roles of motor experience in the context of sound, features of the auditory stimulus, and training constraints could be elucidated to further improve the benefits of music therapy. Research from our laboratory suggests the importance of tailored music therapy programs based on close observation and individual music preferences.

Animal Model of Sound-induced Activation

As the above research highlights, engaging in music can profoundly influence auditory areas of the brain, motor behaviour, and attention or arousal. Despite the rich literature on music and the brain, the underlying mechanism for music-induced movement remains unclear, and an animal model of music-induced benefits in PD has not been developed. Specifically, it is not known if sound induces activation through "classical" auditory-motor connections responsible for defensive behaviour, or if the effect depends on a neural module dedicated to behavioural activation. The roles of motor experience in the context of sound, features of the auditory stimulus, and training constraints could be elucidated to further improve the benefits of music therapy. Research from our laboratory suggests the importance of tailored music therapy programs based on close observation and individual music preferences.

Haloperidol-induced catalepsy

To develop a model of sound induced activation, the present study used neuroleptic-induced catalepsy, a well-characterized model of akinetic catalepsy in advanced PD. Haloperidol, a classical antipsychotic medication, is a dopamine antagonist and binds primarily to D2 receptors of the striatum. The antagonistic action of haloperidol decreases excitation of the motor cortex and in high doses acts as a model of the akinesia seen in advanced human PD, a disease state in which patients can require a movement "trigger" or cue to release them from cataleptic akinesia (Berardelli et al., 2001; Ma et al., 2004). Haloperidol-induced catalepsy can differ in presentation and neural basis from other forms of experimental catalepsy including morphine-induced catalepsy (DeRyck and Teitelbaum, 1983; Koffer, Berney, and Hornykiewicz, 1978) but is similar in behaviour and mechanism to the akinesia observed carbachol infusion into the pontine reticular formation (Koffer et al., 1977; DeRyck et al., 1980) and SCH23390 or Sulpiride administration into the globus pallidus (Hauber and Lutz, 1999). In the haloperidol model, rats are acutely or chronically administered haloperidol, a D2 receptor antagonist, and display immobility at higher doses that exhibits a trial-to-trial increase. The haloperidol-treated rat displays a characteristic stance that protects the rat from postural challenges. EMG recordings of haloperidol-treated rats are comparable to those found in human patients, such that muscle responses to passive movement are delayed, exaggerated, and synchronous (Lorenc-Koci et al., 1996; Burkhardt et al., 2007). Rats lose access to voluntary movement and associated subsystems but can exhibit postural responses (termed release from catalepsy in this thesis) mediated by intact movement subsystems. The sound-induced release of catalepsy has not been documented in the

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literature. Haloperidol-induced catalepsy provides a unique paradigm in which the effect of prior motor training (i.e., moving in response to an activating auditory cue) can then be tested while the animal is in a dopamine-depleted state.

Activating sounds for the rat

The following section will review what is known about specific activating sounds in the rat. Nearly all species of animals, including humans, are activated or aroused by sound stimuli. It appears likely that the nervous system is designed to respond to certain salient sounds with behavioural arousal. Conspecific vocalizations in rats, for example, communicate appetitive or affective states and function to release behavioural sequelae associated with parenting and mating behaviour. Rats vocalize in the sonic and ultrasonic ranges, and produce ultrasonic vocalizations (USVs) that are broadly divided into "22-kHz" (i.e., low frequency) and "55-kHz" (i.e., high frequency) calls that have been related to anxiety- (e.g., isolated rat pup) or fear-related social interactions, and appetitive situations (e.g., in the context of cocaine) or positive social interactions, respectively. There are also reports of naturally produced sound stimuli, such as crumpling tin foil (Whishaw, 1993) and key jingle (Barto, 1957) being applied in spatial memory tasks and audiogenic research, respectively. The sound stimuli used in the studies contained within this thesis employ sounds made from jingling keys, crumpling chip bags (tin foil), single frequencies, and ultrasonic calls made by female rats during sexual encounters with males.

Cephalocaudal recovery of behaviour

The experiments presented in this thesis make use of a movement notation system derived from the Eshkol-Wachman Movement Notation (EWMN) system and a five-point movement score based on cephalocaudal movement of the body during orienting and righting responses. Briefly, EWMN describes the body as a series of limbs, defined as an axis located between two fixed joints, located with horizontal and vertical spheres. This thesis will describe the movement of the body in relation to a body system of reference (SoR) and an external SoR, in relation to the sound source. A number of studies have described the recovery of spontaneous movement following lesions of the lateral hypothalamus, neuroleptic-induced catalepsy, or developmental situations in which infant rats exhibit movement in successive stages (Golani et al., 1981; Teitelbaum et al., 1976)

Theory and Hypotheses

Theory

Music as a familiar auditory stimulus affects a distributed network of auditory and motor areas of the brain, and can be used to help patients overcome slowness of movement.

Hypothesis one

Behaviourally relevant sounds will be activating to a normal rat.

Hypothesis two

Behaviourally relevant sounds will release haloperidol-treated rats from catalepsy.

Hypothesis three

Previous experience with behaviourally relevant sounds will increase potency.

Overview

This thesis will present studies that are qualitative in nature on the movements elicited by behaviourally relevant sounds in the rat. Chapter Two will present an experiment on auditory orienting responses in normal and haloperidol-treated rats to naturally produced (single or multiple key jingle, crinkling chip bag) and generated sound stimuli (frequencies from 500 Hz to 65 kHz and ultrasonic vocalization). Chapter Three will present a series of experiments on a model of sound-induced movement (i.e., release from catalepsy) in a rat model of PD using sound stimuli versus vestibular displacement. Chapter Four will present a set of experiments on release from catalepsy following the presentation of frequencies or rat vocalizations. A general discussion on behavioural activation in PD, as informed by the current experiments, will follow in Chapter Five.

CHAPTER TWO

ORIENTING TO SINGLE FREQUENCIES, KEY JINGLE, CRUMPLING TIN FOIL, AND ULTRASONIC VOCALIZATION: SOUND-INDUCED ACTIVATION IN NORMAL AND HALOPERIDOL-TREATED RATS

ABSTRACT

Central dopaminergic pathways influence the ability of an animal to locate and respond appropriately to novel environmental stimuli. Correspondingly, lesions of the striatum produce deficits in orienting to sensory stimuli and prepulse inhibition deficits. The current study investigated the movements elicited by a range of auditory stimuli including key jingle, crumpling chip bag, ultrasonic vocalization (USV), and single frequencies across the rat hearing range. Saline- and haloperidol-treated rats were placed in an orienting chamber and filmed for orienting responses to novel sounds. A modified EWMN notation score and five-point cephalocaudal orienting scale described the orienting components of both groups. Results showed that key jingle and rat USV were most potent for evoking an orienting response, which was characterized by a characteristic three-stage motor response of Orient, Attend, and Disengage. Further, when responding to frequencies within a 22-kHz band, key jingle, or chip bag, the rat's pinna and not eyes turned in the location of the sound source. These two observations highlight differences in detecting auditory stimuli that can be seen in the orienting phase alone, and provide insight into which sounds might work best as a "cue" for motor tasks.

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INTRODUCTION

Locating communication and environmental sounds in space is a central task of the auditory system and a skill important for guiding normal behaviour (Winer and Schreiner, 2005; Sokolov, 1963). The orienting reflex, as classically identified by Pavlov (1927) and Sokolov (1963), exists as an immediate motor reaction that allows the animal to detect and localize a sudden change in the environment. Intact dopaminergic systems mediate normal behaviourally reactivity to novel sensory stimuli and are important for the survival of an animal (Hall and Schallert, 1988a; Sokolov, 1963; Keller et al., 1983). Lesions to ascending dopaminergic projections produce animals unable to correctly orient their attention to novel sensory stimuli (Marshall and Gotthelf, 1979), or to appropriately disengage or ignore environmental stimuli (Swerdlow and Geyer, 1993; Hall and Schallert, 1988b). Animals with unilateral striatal dopamine depletion show decreased motor responses to contralateral sensory stimuli (Carli, Evenden, and Robbins, 1985). When faced with potent or stressful stimuli, however, rats with 6-OHDA lesions or lateral hypothalamic lesions show a brief recovery of function (e.g., when placed in a pool of cold water, akinetic rats swim vigorously and remain activated for a time), similar to the long-term spontaneous recovery that can occur post lesion (Marshall and Gotthelf, 1979; Teitelbaum, Schallert, and Whishaw, 1983). During continuous performance tasks and signal detection tasks, animals often respond to sensory stimuli with behavioural arousal or task-specific activation (VaezMousavi et al., 2007; Doty and Ferguson-Segall, 1987). As a fixed movement pattern, the orienting reflex serves to direct sensory organs

to the source of stimulation, and changes in this pattern may serve as an index for altered sensorimotor gating or processing (Sokolov, 1960).

A number of animal species, including rats, produce ultrasonic vocalizations (USV) when interacting with conspecifics, when exposed to a predator, when isolated as a pup from the mother, or when treated with carbachol (Fendt, Schwienbacher, and Schnitzler, 2006; Brudzynski and Chiu, 1995; Blanchard et al., 1989; Adler et al., 1979; Tinbergen, 1953). These calls are broadly associated with anxiety- and pleasure-inducing situations, known as "22-kHz" and "50-kHz" calls, respectively (Sadananda, Wöhr, and Schwarting, 2008). A number of studies have studied the effect of USV on rat behaviour (Sadananda, Wöhr, and Schwarting, 2008; Wöhr and Schwarting, 2007). For example, rats decrease activity immediately following presentation of 22-kHz calls, which supports the hypothesis that USV with a dominant frequency of 22-kHz can be related to alarm or predator related calls (Brudzynski and Chiu, 1995). Although 22-kHz and 50-kHz calls produce avoidance and approach, respectively (Sadananda, Wöhr, and Schwarting, 2008), it is not known if rats respond with equivalent activation to all frequencies within the rat hearing range (1000-Hz through 80-kHz; Warfield, 1973), or if some frequencies are more potent for behavioural arousal in normal or dopamine depleted rats.

The current study investigated the orienting reflex of rats immediately following presentation of several sound stimuli, including audible and ultrasonic single frequency, key jingle, crumpling chip bag, and USV playback. Naïve saline- and haloperidol-treated rats were placed in a Plexiglas® orienting chamber and filmed for orienting responses. Movement components were described using movement notation analysis and quantified using a five-point cephalocaudal movement scale. We hypothesized that saline treated

rats would orient with large and quick movements that would position the head toward the sound source, whereas haloperidol-treated rats would show smaller, delayed, and incomplete positioning of the body in relation to the sound source.

MATERIALS AND METHODS

Subjects

Nine male Long-Evans Hooded rats, approximately 6 months old at testing, were obtained from the University of Lethbridge colony where they were housed in pairs in Plexiglas® cages and kept on a 12:12 LD cycle (with dark phase beginning at 7:30pm) with ad libitum access to food and water. Testing was carried out during the light cycle. Experiments were conducted in compliance with the guidelines of the University of Lethbridge animal care committee and the Canadian Council on Animal Care, which complies with international standards for animal care.

Drug

Drug dosage of 5mg/kg of Haloperidol (Sigma-Aldrich) or physiological saline was administered intraperitoneally 20 minutes prior to the testing session.

Apparatus

The orienting chamber consisted of a 48 x 25 x 20 cm Plexiglass® cage (Fig. 2.4, left). Sounds were presented 30 cm to the right side of the chamber.

Video Recording

Rats were video-recorded (30 fr/s) (Sony DCR-VXR 2000 NTSC) laterally for orienting responses once placed inside the apparatus. Video-recordings were used for

offline frame-by-frame movement analysis on a digital videocassette recorder (Sony GV-D1000 NTSC).

Pilot study

Thirty untreated rats were filmed for orienting responses to single frequencies from 500-Hz through to 65500-Hz, at 1-kHz intervals. Rats were singly placed in the orienting chamber, and each presented with 13 sound frequencies once exploration of the cage ceased and the rat was in a quiet waking state. Each group received the same order of sounds. The presentation of each sound frequency was arousal-dependent and did not occur at a fixed interval. The practice of presenting auditory stimuli when the rat was in a quiet resting state was also practiced in the current study.

Group Assignment

In the current study, nine rats were filmed for orienting components to naturally produced or generated sound stimuli following haloperidol (n=5) or saline (n=4) administration.

Testing

Rats were singly placed in the orienting chamber and video-recorded 20 minutes following injection. Saline-treated rats were free to move around the chamber during the testing session. Haloperidol-treated rats were singly placed in the chamber until motor activity decreased and the animals were no longer exploring the cage. Randomized stimuli presentation began once the rat slowed exploration of the cage, was on all fours,

and was not grooming or exhibiting scanning of the head. Stimulus presentation began after the haloperidol-treated rats were in the chamber for 5 minutes, as they remained cataleptic throughout the session. After the presentation of a sound stimulus, the rat was given at least one minute, or time to resume a quiet resting state, before another stimulus was given. If a rat began moving prior to sound presentation, the trial was discarded.

Stimuli were presented by a researcher to the right side of the orienting chamber. Each rat was randomly presented with each 1-second sound stimulus: key jingle, crumpling chip bag, ultrasonic vocalization, 2000 Hz, 12 kHz, 22 kHz, 34 kHz, 44 kHz, 55 kHz. For the key jingle stimulus, a 1-sec burst of eight jingling metal keys was presented (Fig. 2.1). A small bag of Dorito's® chips was crinkled for one second to produce crinkling tin foil sounds. A software based computer system was used to produce single frequencies and USV stimuli (Fig. 2.2) (HP 8903B Audio Analyzer, Alesis RA150 2-channel Amplifier, Monitor Audio Loudspeaker, muRata Manufacturing Co Ltd Tweeter System ES105). For the ultrasonic vocalization stimulus was played at 75dBc through Windows Media Player (Fig. 2.2 top). Single frequencies were produced at 75 dBc using Lab View 8.6 (National Instruments) (Fig. 2.2 bottom). The sound pressure of frequencies to 15 kHz was verified using a Sony BoomStick (SPL1000).
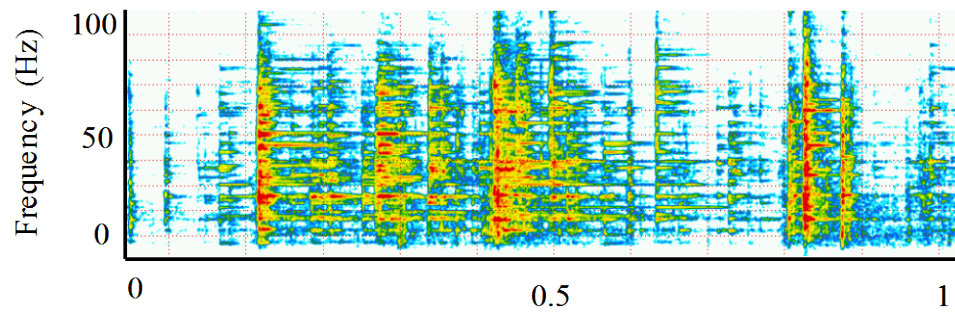
Fig. 2.1. Representative spectrogram for a 1-sec burst of key jingling. Note the strong (red) power spectra at frequencies that cover the rat hearing range.
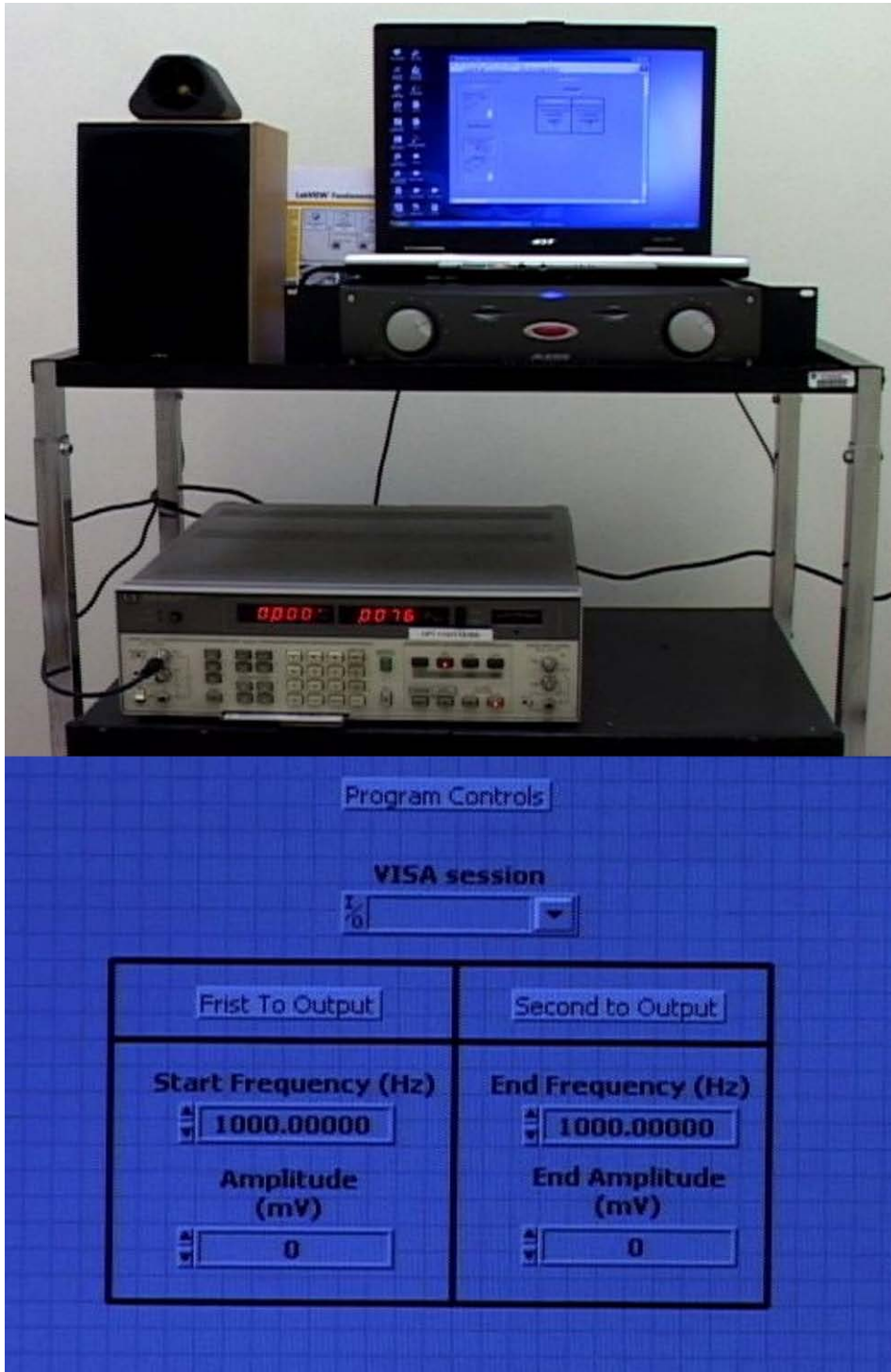
Figure 2.2. Frequency- and USV-generating apparatus. The sound-generating set-up was located to the right of the orienting chamber.

Quantification of Orienting Reflex

Orienting responses were described using a movement scale derived from Eshkol-Wachman Movement Notation (EWMN) and then quantified using a five-point cephalocaudal score. The orienting reflex was measured by documenting the body movements made following onset of the sound stimulus. The duration of time in milliseconds each animal spent in Orient, Attend, and Disengage was noted on each movement score. EWMN conceives of the body as a series of heavy and light limbs (axes located between two joints) that move along points of an external sphere (Fig. 2.3).
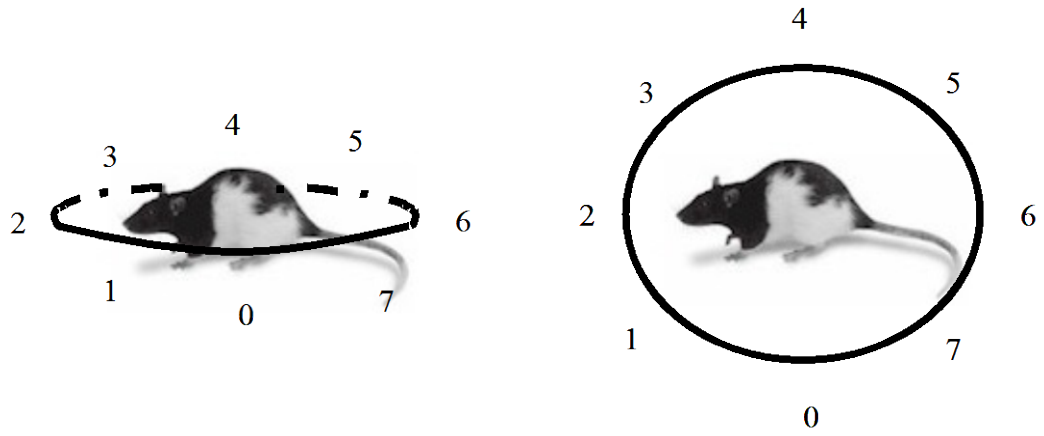
Figure 2.3. EWMN horizontal and vertical spheres of reference. Each of the seven points along the axis (from "0" to "1") designates a movement of 45° along the sphere. Movement of heavy body parts, such as the shoulder, often carry light limbs along for part or all of a movement.

Experimental Procedure

Male rats were handled daily for three minutes for one week and then administered saline or haloperidol twenty minutes prior to the orienting task.

Statistical Analysis

Statistical analysis was performed using SPSS (version 13). In all experiments, repeated measures analysis of variance was conducted to test for main effects of group and stimulus type on orient size. Post hoc analysis used Least Significant Difference with a p value of less than .05 as the criterion for statistical significance.

Block 1:

Hip					
Shoulder					
Hind paw					
Forepaw					
Head	0	1			
	6 →↑	7			
Pinna					

Block 2:

Hip					
Shoulder	1	1			
	6 →	7			
Hind paw					
Forepaw	0	0			
	6 →	7			
Head	0	1			
	6 →↑	7			
Pinna					

Block 3:

Hip	1	1			
	2 →	3			
Shoulder	1	2			
	7 ↑	7			
Hind paw					
Forepaw	0	1			
	7 ↑	7			
Head	1	3			
	7 ↑	7			
Pinna					

Block 4:

Hip					
Shoulder	2	3			
	7 ←↑	6			
Hind paw					
Forepaw	1	3			
	7 ←↑	6			
Head	3	3			
	7 ↑	5			
Pinna					

Figure 2.4. Example movement notation score. The movements taken to reach the posture

seen in each successive video frame are recorded in the associated movement score. Arcs

represent duration of movement. Each numerical pair designates the amount of

movement along the sphere. The top number indicates movement along the vertical axis,

and the lower number indicates horizontal movement. Arrows designate the direction of

movement, with left pointing areas showing counter clockwise movement, right facing

arrows showing clockwise movement.

RESULTS

Pilot Study

       Pilot results indicated that untreated rats could orient to frequencies across the rat

hearing range (500 Hz through 64500 Hz) (Fig. 2.5). For this reason, six frequencies were

chosen at regular intervals for the current study.
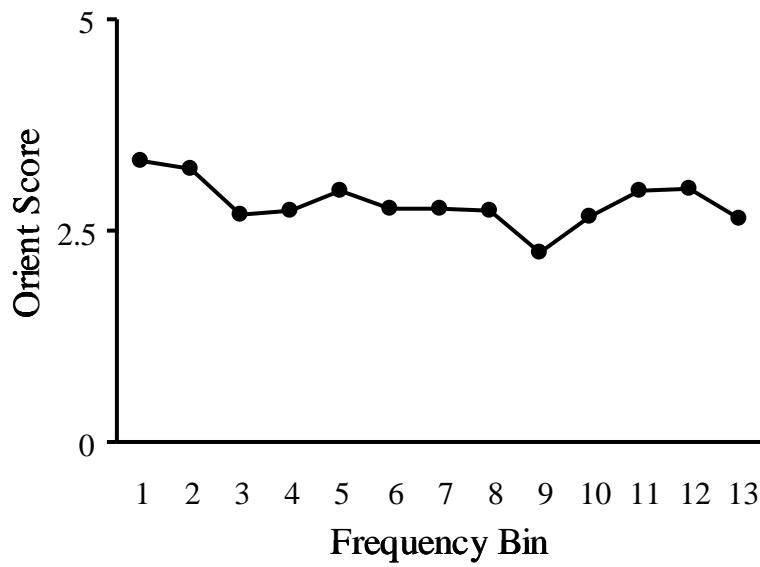
Figure 2.5. Pilot study results (500 through 64500 Hz at 1000 Hz intervals, 75 dBc). Each frequency bin contains 5000 Hz. An orienting score of "1" denotes no movement, a score of "3" indicates movement of the forepaw, and a score of "5" indicates a cephalocaudal orienting response. Untreated rats did not display an absence of orienting to any of the frequencies.

Movement Notation

Offline analysis of orienting components revealed a characteristic cephalocaudal movement to activating sounds (Fig. 2.6 through 2.10). Further, a three-stage orienting response seen in saline-treated rats following key jingle, USV, or chip bag was abolished following haloperidol treatment. With respect to sounds that appeared to be less potent, rats responded only with pricking of the pinna.
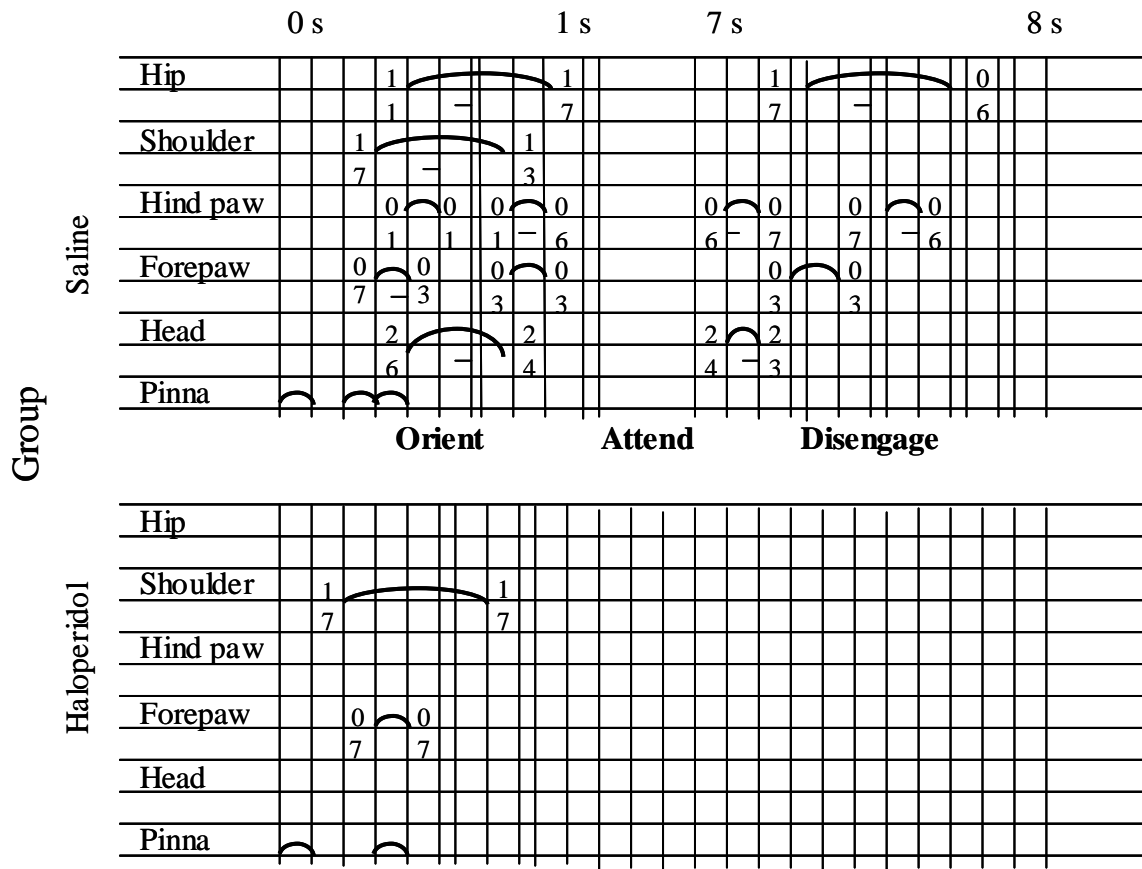
Figure 2.6. Representative movement notation results for Key Jingle. The arcs indicate duration of movement in milliseconds. Key Jingle prompted saline-treated rats to direct the ears and body toward the sound source, and increased locomotion.
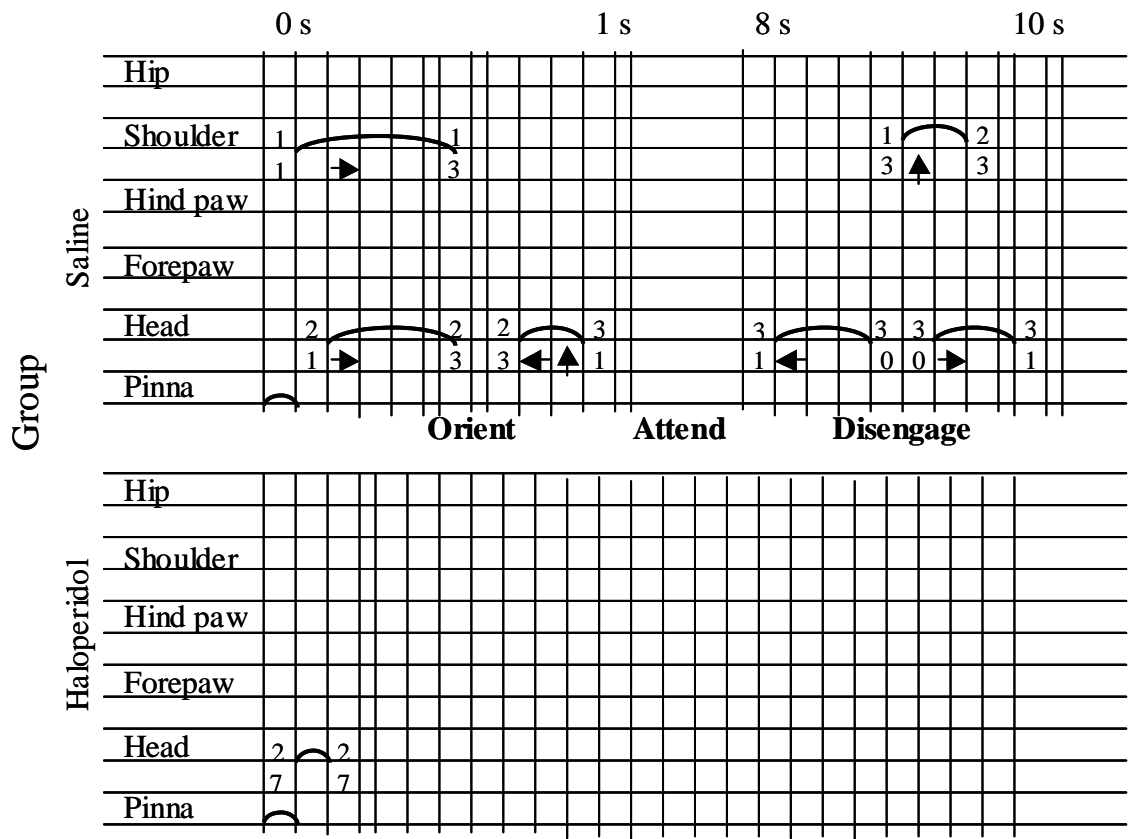
Figure 2.7. Representative movement scores for Crumpling Chip Bag. Saline-treated rats exhibited head scans that were sporadically directed at the sound source.
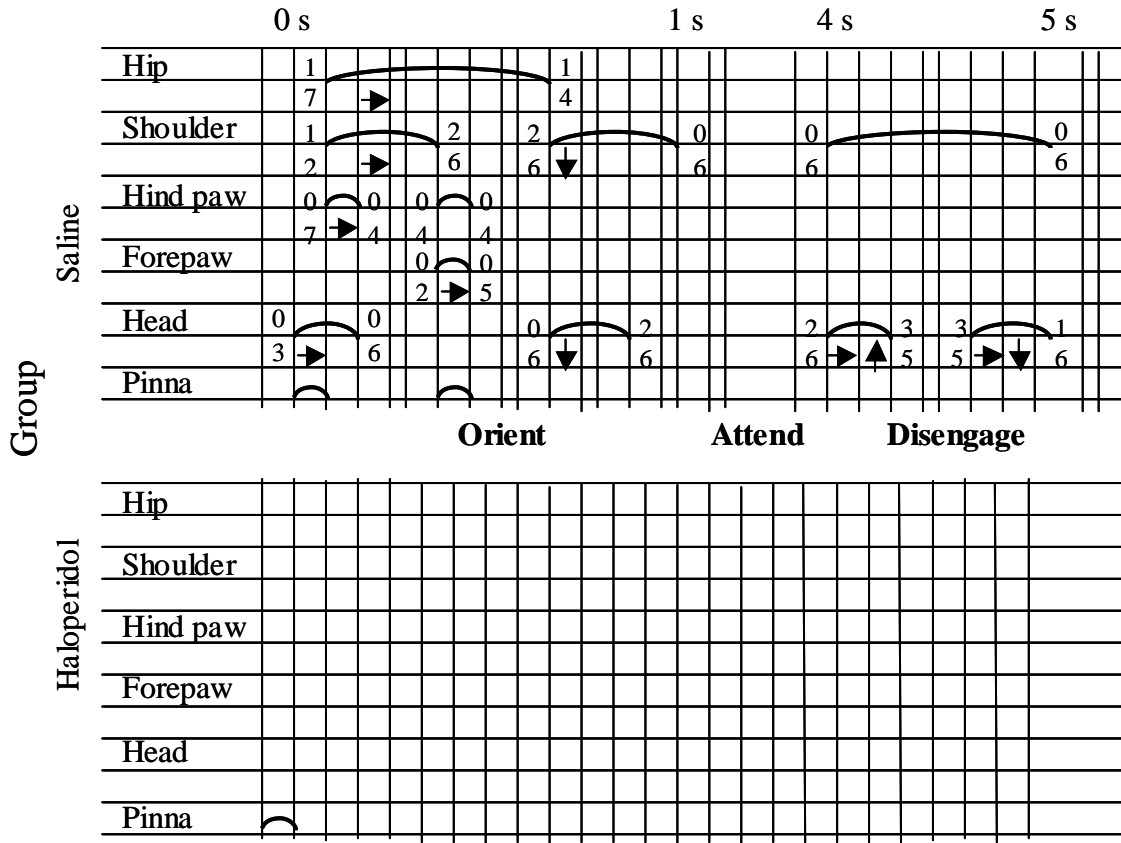
Figure 2.8. Representative movement scores for Ultrasonic Vocalization. USV presentation evoked scanning of the head in the direction of the sound source and increased locomotion. Haloperidol significantly reduced orienting to the USV stimulus.
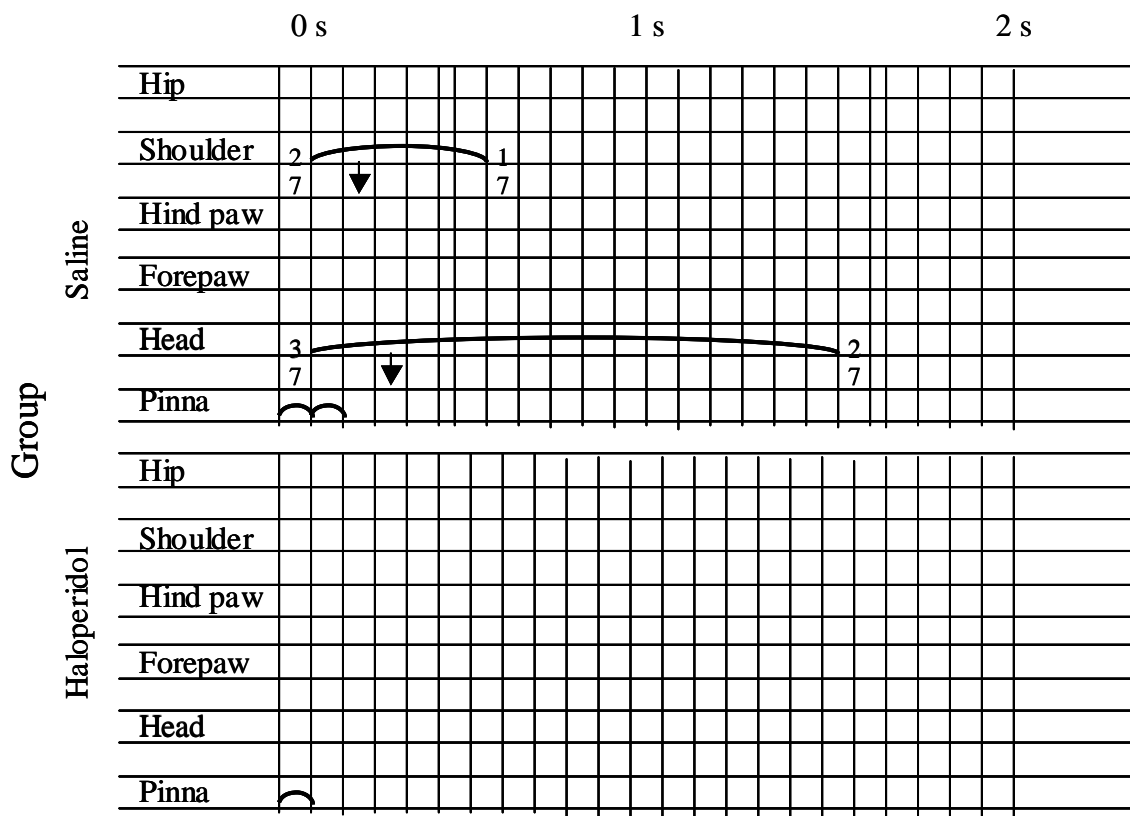
Figure 2.9. Representative movement scores for 22-kHz. Saline-treated rats (top) responded to 22-kHz sound with orienting of the front half of the body and a decrease in locomotion. Note the decreased responsiveness of haloperidol-treated rats.
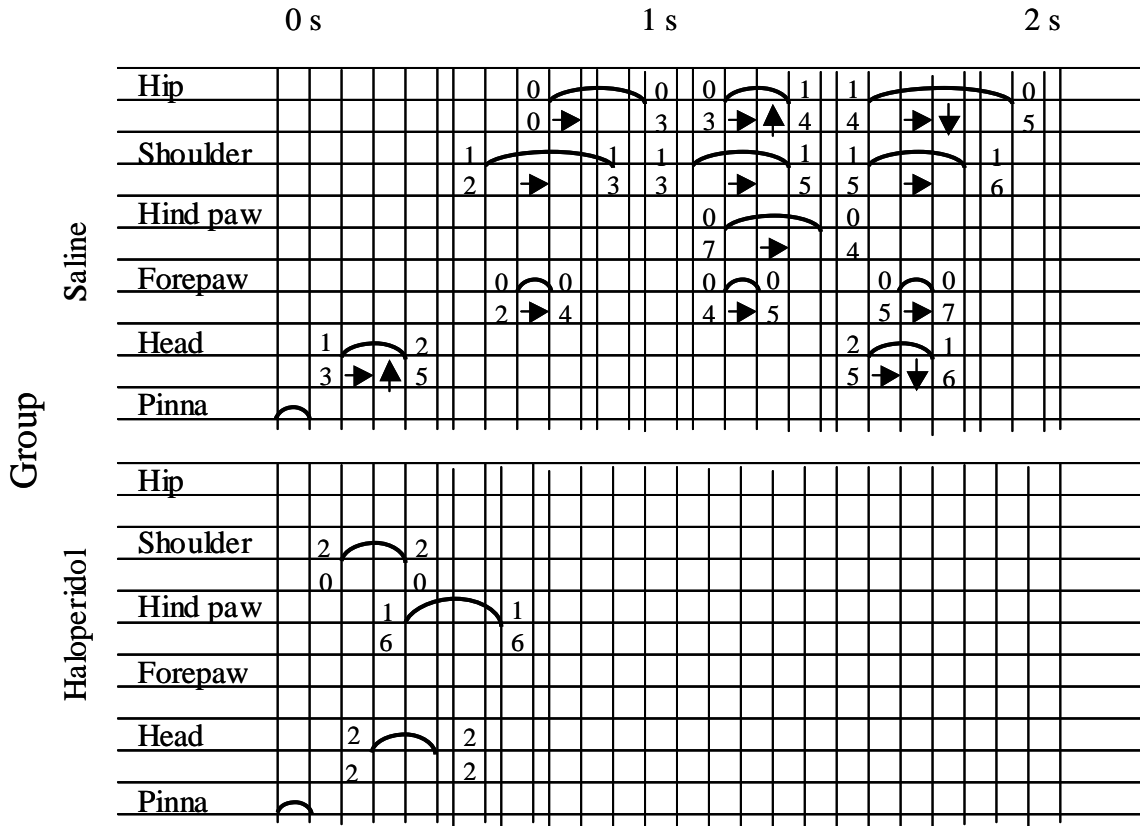
Figure 2.10. Representative movement notation for 55-kHz. Although haloperidol-treated rats did not display orienting movements greater than 45°, they exhibited bracing in the front half of the body.

Cephalocaudal Orienting Score

Endpoint analysis revealed that saline-treated rats did not direct their body equally to all sounds, that haloperidol reduced the responsiveness of rats to all sounds, and that drug treatment did not affect all sounds equally (Fig 2.11 and 2.12).
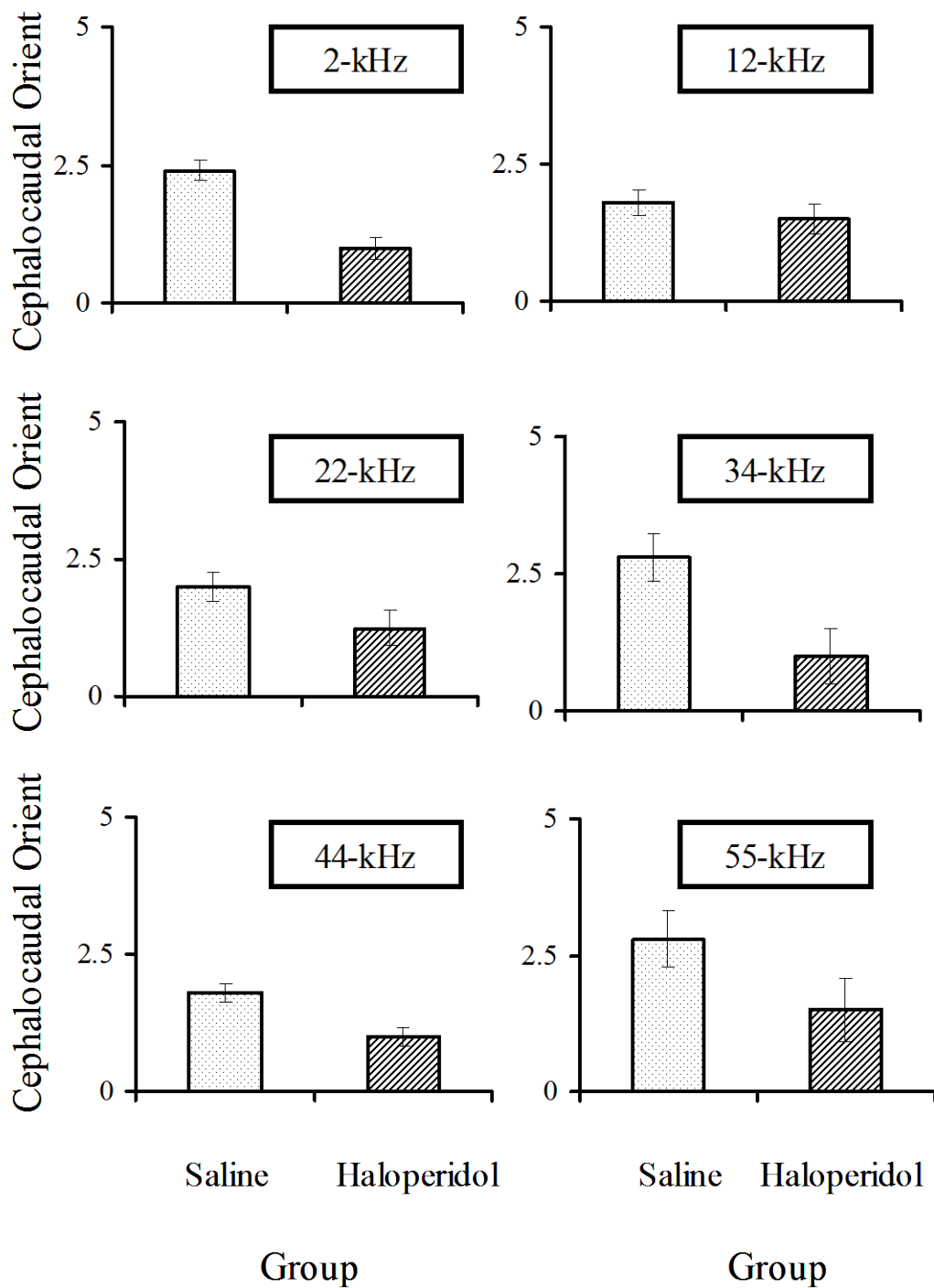
Figure 2.11. Frequency-induced cephalocaudal orienting in saline- and haloperidol-treated rats. A score of "1" denotes no movement, a score of "3" indicates movement of the forepaw, and a score of "5" indicates a cephalocaudal orienting response. Between

groups, haloperidol reduced the occurrence of a cephalocaudal response, such that rats in the treated condition did not respond with more than sway at the front half of the body. Responses to USV and crinkling chip bag stimuli were most susceptible to haloperidol treatment.
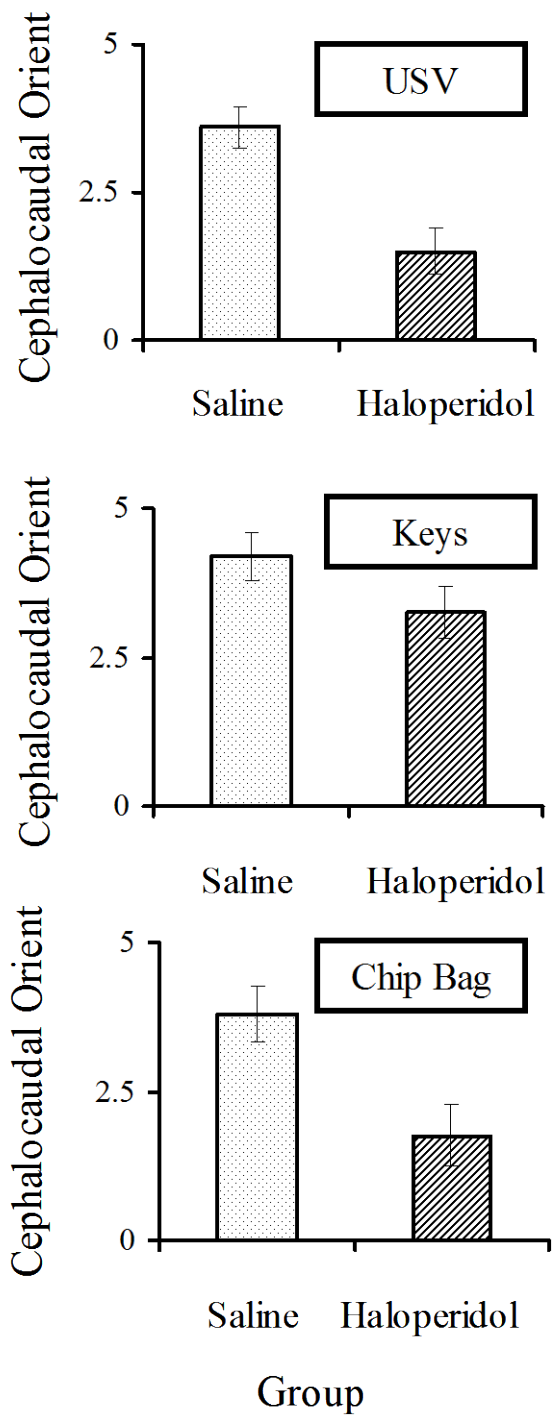
Figure 2.12. Cephalocaudal orienting in saline- and haloperidol-treated rats following key jingle, crinkling chip bag, and ultrasonic vocalization.

DISCUSSION

The current study demonstrated that haloperidol-treated rats do not orient equally in movement components or movement size to the frequencies we presented at intervals across their hearing range, that rats made cataleptic with haloperidol do not display a three-stage orient response seen in saline-treated rats, and that some sounds are more affected by haloperidol treatment than others. The most potent sounds for orienting included key jingle, ultrasonic vocalization, 55 kHz frequency, and crinkling chip bag. Thus, the present study demonstrates the interaction of behavioural responsiveness with altered dopamine transmission in relation to sounds relevant to the rat. The current data can be applied to auditory cueing studies in the normal or haloperidol-treated rat.

The importance of sound for behaviour and communication in many animal species has been documented in natural observation and experimental studies (Gamble, 2008; McCracken and Sheldon, 1997; Sokolov, 1983; Tinbergen, 1953). Classical ethological literature highlights the importance of innate releasing mechanisms for sex – and species-specific behaviour (Lorenz, 1965). For example, female Sticklebacks elicit a zigzag dance in the male Sticklebag that contains a chain of back and forth movements between the two partners. In this way, the female is able to activate a complex zigzag movement chain, derived from movement primitives, guided by an underlying motivation (Tinbergen, 1953). In addition to visual stimuli such as dance, we also find that sound appears to be a source of multiple innate releasers for behaviour in higher order animal species that use sound to communicate. Calls made by the male often serve to attract females and may serve as a signal for fitness (Levitin, 2006). In the mouse, when the

onset of dominant frequencies in an infant mouse call is varied, caring behaviour in the mother fails to be activated (Geissler and Ehret, 2001). Thus, the structure and dominant frequencies of such mating and developmental social calls are important for eliciting the appropriate motor chain and interaction (McCracken and Sheldon, 1997).

Saline-treated rats did not respond to all of the auditory stimuli to the same degree. It is important to note that key central nervous systems regions that are known to mediate motivation (and activation) also mediate the production and responsiveness to sound communication. The current study is the first to make note of differential orienting responses to stimuli within the same sensory modality (i.e., auditory). Saline-treated rats displayed the highest levels of detection in response to a USV elicited during a precontact mating encounter, pleasure-related frequencies near 50 kHz as well as sounds produced by jingling keys and crinkling tin foil. Thus, auditory stimuli that have previously been characterized as having "activating" properties for the rat were found to be most potent for causing rats to orient.

A second finding from the current study indicated that haloperidol does not reduce responsiveness to all activating stimuli equally. Correspondingly, lesions to central DA pathways produce altered responses to sensory stimuli in dopamine-depleted animals (Teitelbaum, Schallert, and Whishaw, 1983) and patients with Huntington's disease (Swerdlow et al., 1995) or Parkinson's disease (Boecker et al., 1999). After haloperidol treatment, rats displayed blunted motor responses to activating stimuli that had produced complete cephalocaudal movements in saline-treated rats. Haloperidol-treated rats did not orient the head and body toward the sound source. Instead, the treated rats remained stationary and displayed small bracing movements at the forepaw and

shoulder. The interaction of drug treatment with sound cue provides an interesting observation; the key jingle and 22 kHz stimuli appeared to be more resilient to the drug treatment, and the crinkling chip bag, 55 kHz, and USV appeared to be more susceptible to blunted responsiveness under drug. One could interpret that the key jingle stimulus and 22 kHz frequency involve subcortical regions, such as the inferior colliculus, that are known to mediate defensive responses, or behaviours that quickly detect changes in the environment. Conversely, USV, 55 kHz, and sounds produced by tin foil have lower power spectra than the key jingle and a less abrupt sound onset, and are thus less "potent" in terms of overall frequency spectra and sound onset. Future work using this task could increase the ethological validity of the USV cue and present an associated olfactory cue.

A third finding from the current study demonstrated qualitative changes in the orienting response following DA antagonism. Movement notation analysis of normal rats revealed a characteristic three-stage motor response in which the animal first moved the body, and particularly the pinna, in the direction of the sound source ("Orient"). The second stage was marked by immobility in which the pinna remained in the direction of the sound source ("Attend"). Third, the rat would quickly and successively move the head, shoulder, and hip away from the posture held during Attend. Following sound cue onset, rats responded with movement of the pinna, lateral movement of the shoulder followed shortly by lifting and stepping of the forepaw, and subsequent rotation of the shoulder and hip. Independent movement of the head occurred early during Orient and also when the shoulder slowed. Movement notation analysis showed an absence of this three-stage response in haloperidol-treated rats. It is possible that treated rats were unable to move and thus simply could not display a cephalocaudal movement of the body. A

second possibility is that the motor chain responsible for orienting movements was not accessible due to insufficient activation of the striatum. Previously, DA depletion of the striatum has been shown to produce sequential deficits in syntactic movement chains such as grooming (Whishaw and Berridge, 1992).

A novel observation made during the current study was that when a complete cephalocaudal response was observed (in the case of 55 kHz, key jingle, USV, and chip bag), rats would guide the pinna toward the sound source. Consistent with Pavlov's (1927) classical definition of the orienting reflex as a response important for object detection and guidance of the relevant sensory apparatus to the stimulus source, the pinna and not the eyes were primarily involved. Based on pilot observations in our own laboratory, sounds produced by ripping paper towel prompted rats to orient to face the location of the sound origin. Sokolov and his colleagues (2001) propose a two-part orienting reflex consistent with our observations, in which two behavioural responses work to enhance response to relevant sensory stimuli. First, the relevant sensory organ (i.e., ear) was aimed in the direction of the sound source (i.e., "targeting reaction"), and did not reliably include the animal looking directly in the direction of the cue. Second, neural responses to the sensory cue are enhanced, leading to enhanced attention that serves to redirect behaviour in relation to a novel cue in order to maximize memory formation. Thus, as a mechanism to activate and direct attention, the orienting reflex will vary according to the novelty, significance, and intensity of the auditory target (Barry, 1982; Cohen, 1973; Sokolov, 1963).

In conclusion, the current findings revealed qualitative changes in the auditory orienting response following acute haloperidol treatment. We also demonstrated that rats

respond differently to different behaviourally relevant sounds. In conclusion, intact or

impaired DA transmission interacts with the environment to mediate normal behaviour.

CHAPTER THREE

ACTIVATION FROM CATALEPSY IN MALE AND FEMALE RATS WITH NOVEL

AND FAMILIAR KEY JINGLE OR CRUMPLING TIN FOIL VERSUS VESTIBULAR

STIMULATION: A MODEL OF MUSIC-INDUCED IMPROVEMENT IN

PARKINSON'S DISEASE

ABSTRACT

External cues including familiar music can release Parkinson's disease patients from catalepsy but the neural basis of the effect is not well understood. The purpose of the present study was to develop an animal model of sound-induced behavioural activation that could be used to investigate the underlying neural mechanisms. The potency of novel versus familiar sound stimuli on release from haloperidol-induced (5 mg/kg) catalepsy was investigated in the rat in two experiments. Righting response to an auditory stimulus (single key jingle or multiple key jingles) was compared to angular change of an inclined grid in rats that were naïve or familiar with the stimuli. A movement rating system based on Eshkol-Wachman Movement Notation (EWMN) score was used to describe the size and speed of components of the righting response to cue presentation. Release from catalepsy was prompted by postural displacement and the auditory cue, familiar stimuli were more effective than unfamiliar stimuli, and the auditory cue produced a more normal temporal coupling of trunk and limb movements. Findings demonstrate we have developed a rat model of sound-induced behavioural activation that can be used to study the role of experience, sound, and neural mechanisms responsible for the therapeutic effect of music for Parkinson's disease.

INTRODUCTION

The gradual loss of nigral dopamine in Parkinson's disease (PD) is related to the progressive and lasting changes in spontaneous movement including bradykinesia and catalepsy (Marsden, 1990). A number of reports indicate that auditory cueing can help PD patients overcome impairments in initiating movement and normalize their movements (Thaut, 2003; Suteerawattananon et al., 2004; del Olmo et al., 2006). PD is also likely associated with abnormal activation of motor cortex and spinal motor units during rest and movement (Parr-Brownlie and Hyland, 2005), and external cueing normalizes neural recruitment in both humans and non-human animals, possibly by bypassing deficient projections of the basal ganglia (BG) to the supplementary motor area (SMA) (Cunnington et al., 1995). Auditory rhythm has an immediate entrainment effect on the kinematics and electromyographic (EMG) activity of rhythmic motor behaviours such as gait (Thaut et al., 2003) and non-rhythmic movements such as reaching to a target (Thaut and Kenyon, 2003), and can also have a training effect in normal controls and PD patients (Thaut et al., 1996). Presumably, the sensitivity of the motor system to auditory projections at the level of the forebrain, brainstem, and spinal cord provides a mechanism for motor improvements following short- or long-term auditory stimulation (Cunnington et al., 1995; Thaut et al., 1999; Warren, Wise, and Warren, 2005; Chester, Turnbull, and Kozey, 2006). Clinical reports indicate that previous motoric experience likely contributes to the therapeutic effect of auditory cueing in PD by serving as a timekeeper for improved spatiotemporal organization throughout a movement sequence, and by

providing rhythmic auditory input which may decrease catalepsy and "prime" or activate movement (Thaut et al., 2001; Ma et al., 2004).

Although it is well known that listening to and performing music involves distributed areas of the brain (Peretz, 2002; Thaut, 2003; Schuppert et al., 2000), an animal model of music-induced benefits in PD has not been developed. To inform music therapies, the contribution of experience, sound features, and neural mechanisms should be clarified. Sacks (1971) observed that not all music is best for releasing PD patients from akinesia. For example, heavily percussive music may prompt jerky and disconnected movements. Experience (i.e., familiarity) with auditory cues is an additional contributor to the positive effect of music. Human PD patients often go about their activities of daily living in the presence of music, such that they are establish their preferred music preceding disease onset, sometimes by many years. Thus, an animal model of sound-induced behavioural activation should consider the familiarity and acoustic features of the auditory cue.

In order to develop a model of sound induced activation the present study used haloperidol, the present study administered a dopamine antagonist to male and female rats in order to produce a catalepsy model of PD. In neuroleptic-induced catalepsy, animals lose access to voluntary movement and associated subsystems but exhibit righting responses (i.e., release from catalepsy) following presentation of vestibular (physical displacement) or other sensory stimuli (De Ryck, Schallert, and Teitelbaum, 1980; Teitelbaum, Schallert, and Whishaw, 1983; Field, Whishaw, and Pellis, 2000). EMG recordings of haloperidol-treated rats are comparable to those found in human patients, and indicate a delayed, exaggerated, and synchronous muscular and neural

response to passive limb and trunk movement (Lorenc-Koci et al., 1996; Burkhardt et al., 2007). Dopamine transmission of the basal ganglia mediates the force and initiation of well-learned movements, and acts as a permissive learning signal for associations that can be accessed for a time while in a dopamine depleted state (Beninger, 1983; Schmidt and Beninger, 2006). Further, motor experience prior to 6-hydroxydopamine lesions in rats has been associated with an increase in plastic processes and improved post-lesion performance (Cohen et al., 2003). Thus, this model investigated the effect of prior motor training (i.e., moving in response to an activating auditory cue) on subsequent movement performance in a dopamine-depleted state.

In the current model, normal rats were given three days of task experience, consisting of six randomized stimulus presentations (three sound and three tilt) over five minutes, or habituation (in the absence of stimuli) to a wire grid box. Experienced and naïve rats were then administered haloperidol and were presented with physical displacement alone (control tilt stimulus) or auditory stimulation alone (single 1-sec key jingle or five repeated bursts of key jingle). Stimuli-induced righting responses were filmed for offline frame-by-frame analysis of size of righting response and righting components. Results revealed that auditory cues could overcome catalepsy, and experience with the auditory cue further normalized movements.

MATERIALS AND METHODS

Subjects

Seventy-seven Long-Evans Hooded rats, approximately 4 months old at testing, were obtained from the University of Lethbridge colony where they were housed in pairs in Plexiglas® cages and kept on a 12:12 LD cycle (with dark phase beginning at 7:30pm) with ad libitum access to food and water. Prior to testing each rat received about 3 min of handling in the colony room for one week and 3 min of handling in the test room for one additional day. Handling consisted of picking up the rat from its cage and replacing it a number of times. Testing was carried out during the light cycle. Experiments were conducted in compliance with the guidelines of the University of Lethbridge animal care committee and the Canadian Council on Animal Care, which complies with international standards for animal care.

Drug

Drug dosage of 5mg/kg of Haloperidol (Sigma-Aldrich) was administered intraperitoneally 20 minutes prior to the righting trials. Saline controls received an equivalent volume of physiological saline. All injections were administered during the testing session and not during training sessions.

Apparatus

The grid box apparatus consisted of a rectangular metal grid cage (30cm x 65cm x 15cm) secured to a Plexiglas® base (Figure 3.1, top). The grid box could be manually tilted by a lever (20cm in length) attached to the left side of the cage. A protractor (90°) was affixed below the lever (Figure 1, bottom) via which to monitor tilt angle. The

apparatus was placed on the edge of a one-meter high table and could tilt away from the edge of the table over a padded elevated surface.
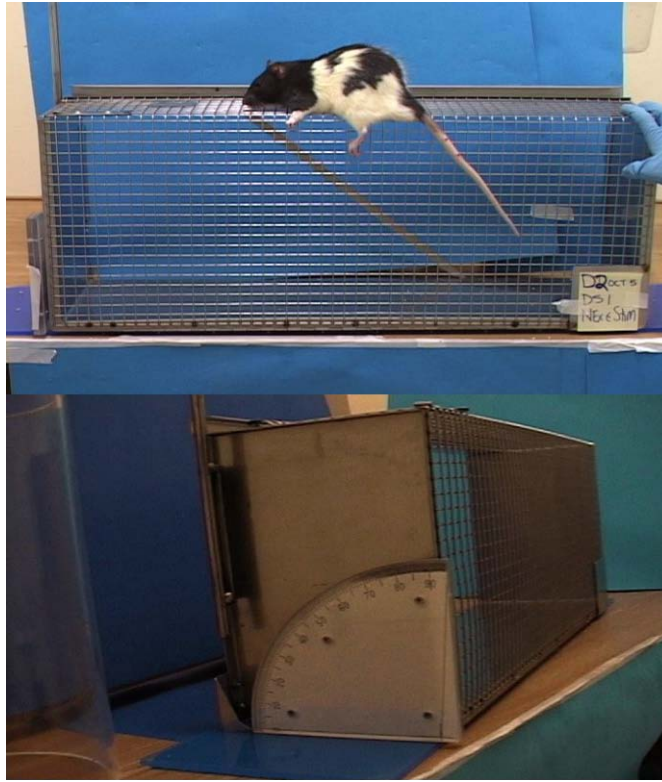
Figure 3.1. Grid box apparatus. Top: Cataleptic rat on the gird in the testing position.

Bottom: Lateral view of the grid showing the protractor for measuring grid incline.

Video Recording

Rats were video-recorded (30fr/s) laterally for stimuli-induced movements during testing. A second video camera filmed the tilt angle of the apparatus. Video-recordings of the lateral view of the rat were used for offline frame-by-frame analysis on a digital video cassette recorder (Sony, GV-D1000 NTSC).

Group Assignment

Experiment one. In experiment one, 33 male rats were assigned to six groups to test for effect of cue familiarity: 1) Naïve saline controls (n=6; explored the horizontal surface of the grid for three minutes daily over three days in the absence of tilt and sound stimuli, and were then tested for righting without cues following saline injection); 2) "No stimulus" haloperidol-treated rats (n=4; naïve rats that were made cataleptic and not given tilt or sound stimuli) 3) Single naïve haloperidol-treated rats (n=6; explored the horizontal surface of the grid without drug for 3 days and were then tested under drug with tilt stimulus and a single 1-second key jingle); 4) Single experienced haloperidol-treated rats (n=5; received three days of tilt and 1-second key jingle experience on the grid box without drug, consisting of three random tilt and three random sound presentations over three minutes, and were then tested with stimuli under haloperidol); 4) Naïve multiple haloperidol-treated rats (n=4; explored the horizontal surface of the grid without drug for 3 days and were then tested under drug with tilt stimulus and multiple short bursts of key jingle); and 6) Experienced multiple haloperidol rats (n=4; received three days of tilt and multiple short bursts of key jingle experience on the grid box

without drug, consisting of three tilt and three sound presentations over three minutes, and were then tested with stimuli under haloperidol).

Experiment two. In experiment two, 21 male rats were assigned to four groups to investigate whether experience with one sound would transfer to a different sound under drug: 1) Experienced with chips (n=6; received three days of tilt and 1-second crumpling chip bag experience on the grid box without drug, consisting of three random tilt and three random sound presentations over three minutes, and were then tested with tilt and chip bag stimuli under haloperidol) 2) Experienced with keys (n=5; received three days of tilt and 1-second key jingle experience followed by testing under haloperidol with the tilt and key jingle stimuli); 3) Tested with chip bag (n=5; received three days experience with tilt and chip bag stimuli and were then tested under haloperidol with tilt and chip bag stimuli); and 4) Tested with key jingle (n=5; received three days experience with tilt and chip bag stimuli and were then tested under haloperidol with tilt and key jingle stimuli.

Experiment three. In experiment three, 11 male and 12 female rats were assigned to each of the following four groups to test for sex differences in righting to a single burst of 1-second key jingle under drug: 1) Naïve males (n=6); 2) Experienced males (n=5); 3) Naïve females (n=6); and 4) Experienced females (n=6). All rats were given context habituation or experience according to the protocol described in experiment one.

Evaluation of Catalepsy

Catalepsy was evaluated by the latency to initiate movement of the limbs or trunk away from the start position (minimum criteria was 30 seconds, to a possible maximum

of 60 seconds). Using a minimum 30-second latency, normal rats do not display catalepsy (Kuschinsky and Hornykiewicz, 1972). Rats were placed on the grid box with one forelimb and the ipsilateral hind limb suspended over the vertical wall of the cage, with the nose placed at a 45o angle to the body to produce slight curvature of the trunk (testing position) (Figure 3.1, top). If a haloperidol-treated rat immediately turned away from the side of the cage and brought both ipsilateral paws to the grid surface, or if they exhibited a low intensity of muscular rigidity (evaluated qualitatively), the animal was returned to a transfer cage for an additional three minutes before subsequent testing, and this was repeated until catalepsy was reached. Righting trials began directly after catalepsy evaluation.

Sensory Stimuli

For the righting response test, rats received no cue, or vestibular and auditory stimuli. Of the eight trials for the "stimulus" groups, four trials were tilt cued and four were sound cued. The sequence for each rat was different.

(1) Vestibular stimulus

For the vestibular stimulus, the grid box tilted at a rate of 2° per second to a maximum of 40 degrees or until the rat righted by brining all four feet to the horizontal surface of the grid. Tilt of the grid box at 2° per second was time-synched with a clock. If a trial provided vestibular displacement greater than 2° per second, the trial was discarded.

(2) Auditory stimuli

For the single key jingle auditory stimulus, a 1-sec burst of eight jingling metal keys was presented five inches behind rats at ear level. For the multiple key jingle stimulus, five bursts of <1-second key jingle were presented to rats across 20 seconds. A second researcher, blind to the experimental group of each animal, jingled the set of keys.

Quantification of Righting

The righting response was measured by noting the body movement made to regain posture on the vertical surface of the grid box in relation to time of the response. From the video record the time at which a rat initiated and completed a Hip, Shoulder, Hind Paw, Forepaw, Head movement was recorded and notated on a time-line chart (Fig. 3.3). For quantification the individual movements were labeled from 1-5, with 1 being a head movement and a 5 being a complete righting response.
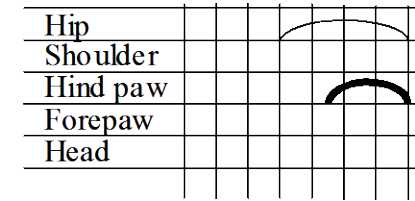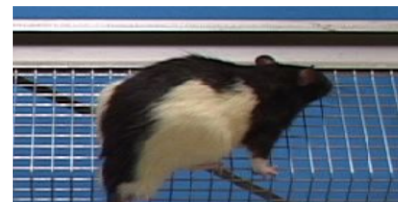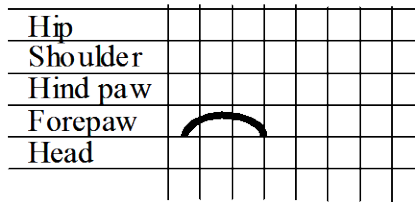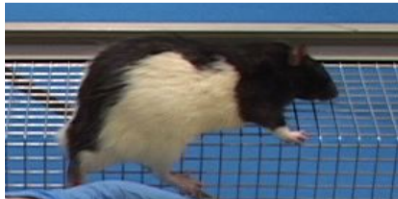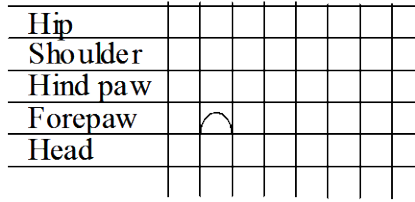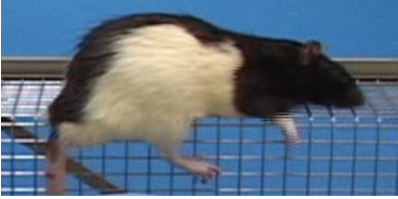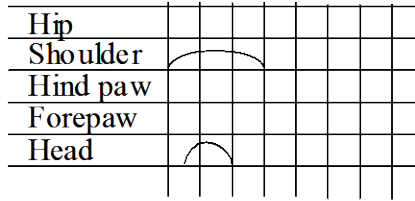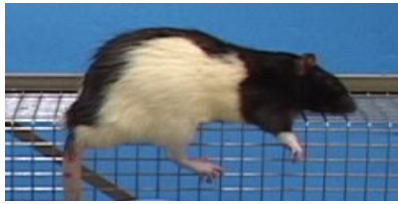
Figure 3.2. Measurement scores for five components of a righting response. Left: Photos illustrate the final position of movements of the Head, Forepaw, Hind paw, Shoulder, and Hip. Right: Score of righting response components. Vertical bars represent units of time (milliseconds). The arcs represent movements and their durations. Darkened arcs show paw placement.

Experimental Procedure

The following was applied to all experiments: 1) rats were handled for one week prior to experience or habituation sessions; 2) saline controls and drug controls were not presented with sensory cues during testing. In experiment one, male rats were handled and then given either experience with the vestibular and auditory cue (key jingle) cue and key jingle or crinkling chip bag auditory cues during grid climbing (or free exploration of the grid box alone for five minutes, in the case of naïve groups) to either chips or keys and then tested under haloperidol with the familiar sound.

Statistical Analysis

Statistical analysis was performed using SPSS (version 13). In all experiments, repeated measures analysis of variance was conducted to test for main effects of group and stimulus type on righting size. Post hoc analysis used Least Significant Difference with a p value of less than .05 as the criterion for statistical significance. A correlation was conducted on complete righting responses of five rats in experiment one using Pearson's r correlation between tilt angle and movement of each body segment, and between latency from sound cue onset and each body segment.

RESULTS

Offline kinematic analyses indicated that vestibular and auditory cues prompted cephalocaudal righting in saline- and haloperidol-treated rats. A familiar versus novel auditory cue was more potent for eliciting righting (single or multiple key jingles), and

the auditory cue prompted a "more normal" temporal coupling of limb and trunk movements than the vestibular cue. Following presentation of the auditory cue, pinna erection toward the sound source was often observed. For vestibular and auditory stimuli, righting was characterized by movement of the shoulder away from the edge of the apparatus, which allowed the rat to flex (lift) the forepaw vertically before moving it medially to contact the surface. Once adducted at the shoulder, the forepaw supported and propelled the body forward, to allow for movement of the hip and hind paw.

Movement Notation

Movement notation results from experiment one score showed differences in the speed and duration of elicited righting (Fig. 3.3). When placed on the grid box, saline-treated rats righted immediately. "No stimulus" drug-treated controls did not right within 20 seconds of being placed. Clear differences were observed between tilt and sound trials, with tilt- induced righting responses being longer in duration and characterized by discrete movements of the Head, Shoulder, Forelimb, Hip, and Hind limb. Although not as reliable as tilt-induced righting, sound-induced righting in rats that were tested with familiar sounds was complete, continuous, and quick, particularly the single burst of key jingle.
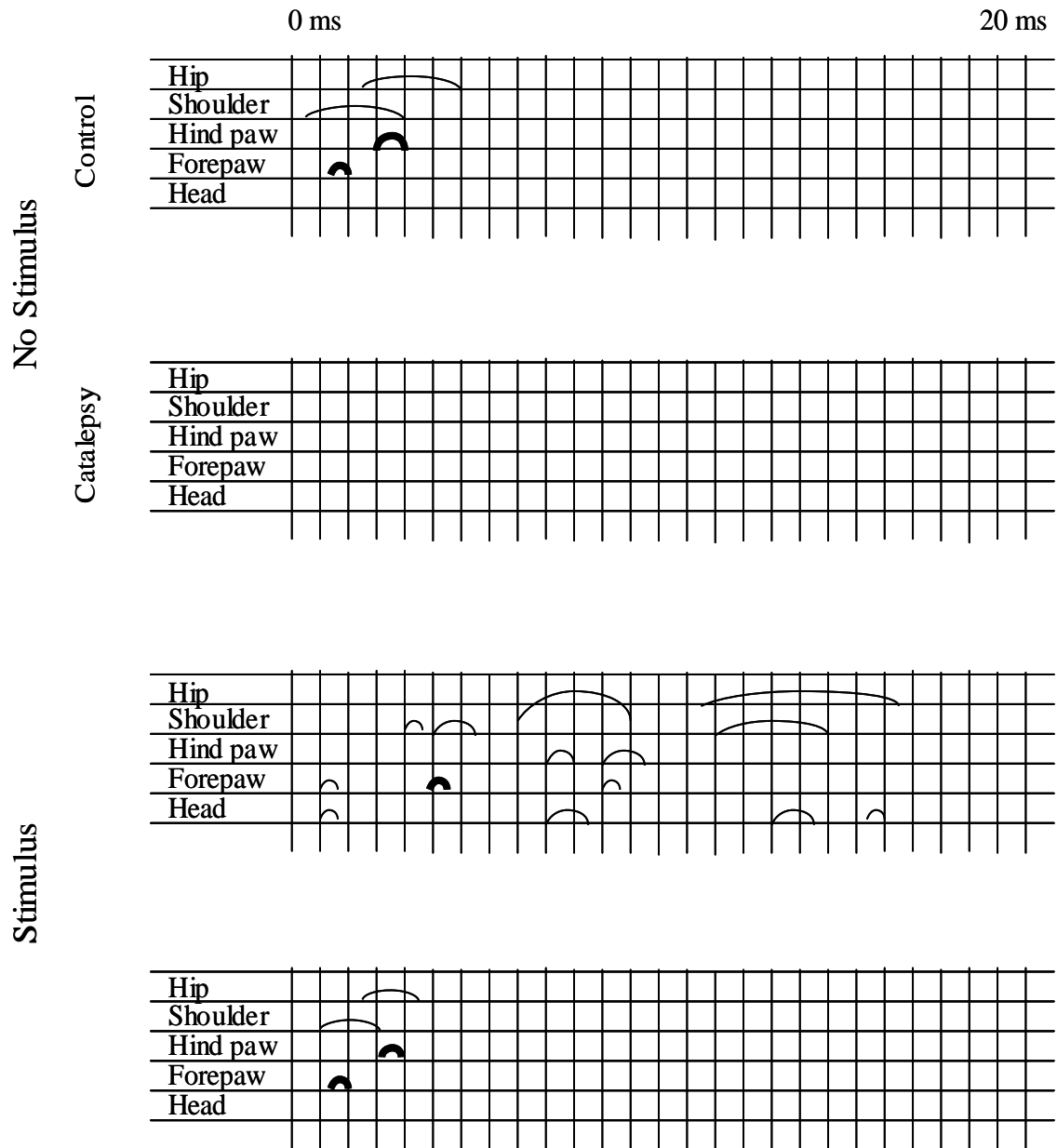
Figure 3.3. Representative movement scores for control and familiar haloperidol-treated rats in no stimulus and stimulus conditions. The arcs show duration of movement in milliseconds. Note rapid righting in a control rat versus no righting under haloperidol in the absence of sensory cues (top), and slow righting to tilt versus rapid righting to sound in cataleptic rats.

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Correlation

The present method allowed for precise control of physical destabilization, and auditory cue presentation, on a single apparatus. Figure 3.4 shows the temporal coupling of righting responses of experienced and naïve rats in response to the tilt stimulus or single key jingle. Righting components were significantly correlated with the angle of tilt (r=.81) and latency from auditory cue (r=.81). The auditory cue produced a normalized temporal coupling of trunk and limb movements.
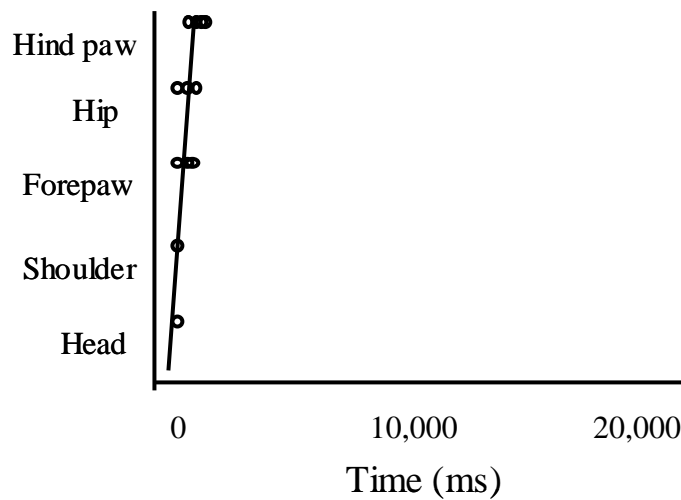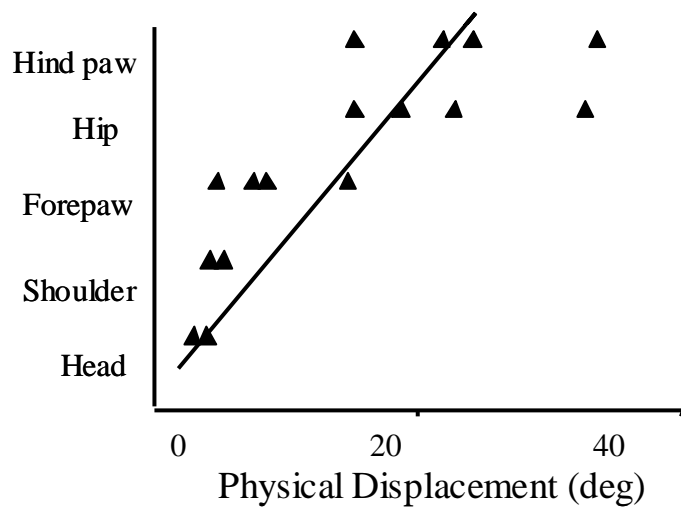
Figure 3.4. Correlation results. Top: correlation in five experienced rats between movements of body parts in relation to tilt of 40 degrees applied over 20 sec. Bottom: correlation between movements of body parts in relation to 1-sec key jingling, standardized to 20 seconds. Note the slow versus rapid response in the two conditions.

Size of Righting Response

In experiment one, the rats that received saline immediately righted whereas the group that received haloperidol in the absence of sensory cues displayed no righting for the duration of each test trial. These levels of performance are illustrated by the dotted lines in Figure 3.5. There was a significant effect of Group on the size of righting responses, $F(4,48)=115.622$, $p<.001$. In the groups there was a significant effect of Stimulus on the size of righting, $F(1,48)=302.224$, $p<.001$. The interaction between Group and Stimulus was significant, $F(3,48)=3.782$, $p<.05$.
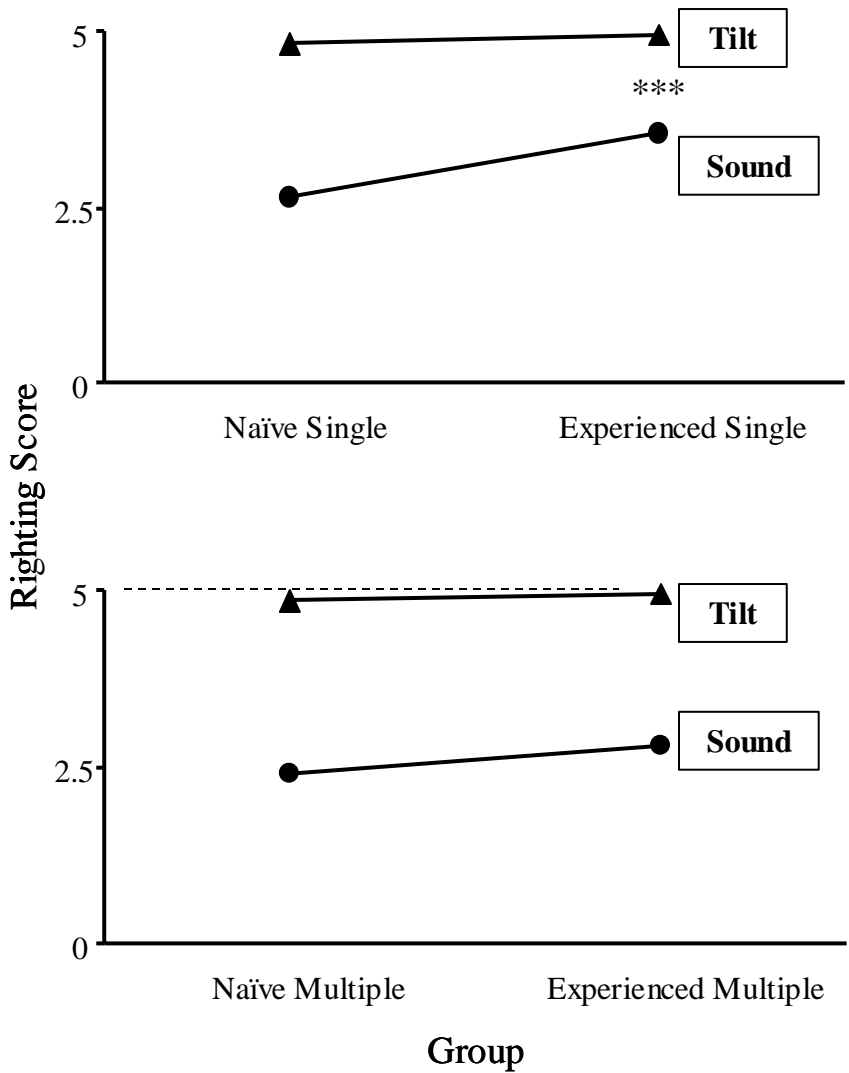
Figure 3.5. Righting size for single or multiple key jingle. Response size (mean and standard error) for naïve and experienced rats reacting to a tilt and sound stimulus. The upper dotted lines show the righting response of saline-treated rats without cues, and the lower dotted lines is the response of haloperidol treated rats with no stimuli. *** denotes p<.001. Top graph: experiment one results. Familiarity with the single auditory cue improved the size of righting responses. Bottom graph: results with multiple bursts of key jingle (analogous to an ongoing musical stimulus). Rats familiar with the single and

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multiple key jingle responded with larger righting movements. Presentation of multiple

key jingle did not increase righting beyond that elicited by a single burst of key jingle.

In experiment two, there was a significant effect of Group on righting size, $F(3,34)=9.37$, $p<.001$ (Fig. 3.6). There was a significant effect of Stimulus on righting size, $F(1,34)=206.215$, $p<.001$. Analysis also revealed a significant interaction of Group and Stimulus, $F(3,34)=8.725$, $p<.001$.
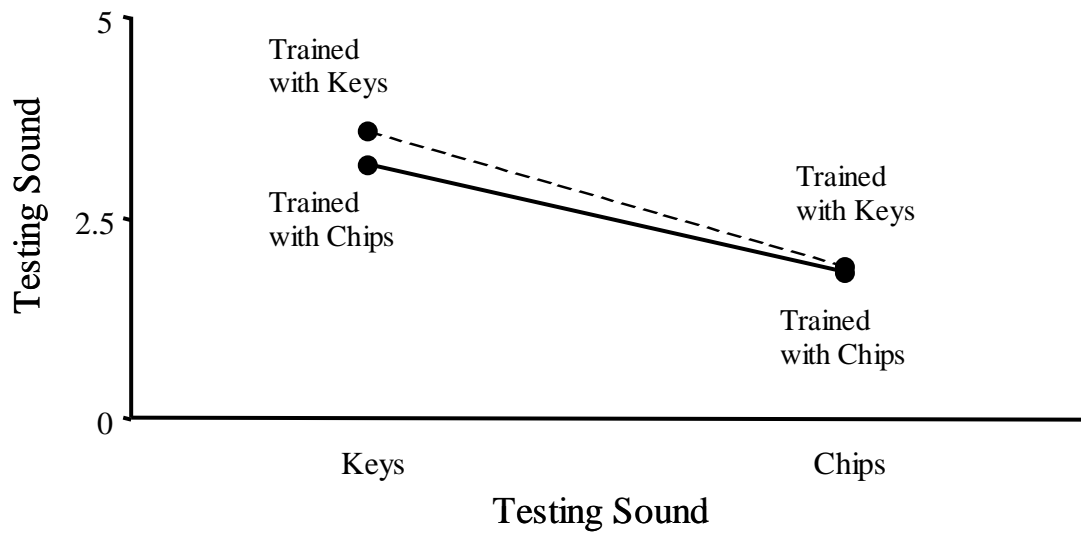
Figure 3.6. Righting size for congruent and incongruent stimuli. Experiment two results for auditory trials. The sound used during testing is along the x-axis. Rats that were experienced with chips or keys but tested with keys did better than rats who were tested with crumpling chip bag sounds. Rats that were trained with key jingle but then tested with crinkling chip bag performed significantly worse than those trained with keys.

In experiment three, there was a significant effect of Group on righting size, $F(3,38)=5.305$, $p<.05$ (Fig. 3.7). There was a significant effect of Stimulus, $F(1,38)=203.421$, $p<.001$. A Group by Stimulus interaction was significant, $F(3,38)=6.311$, $p<.001$.
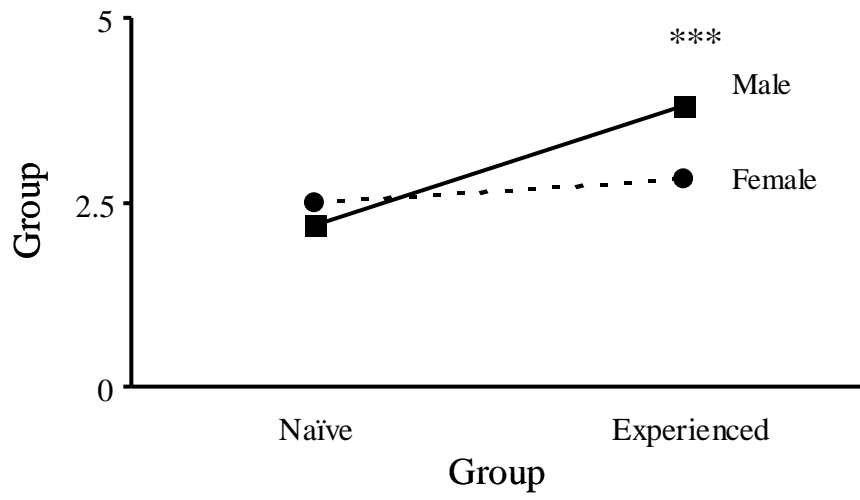
Figure 3.7. Righting size of males and females. Males significantly improved righting size with training, whereas females were not helped by experience with the auditory cue.

DISCUSSION

The present study demonstrated that sound improved the size and temporal coupling of righting responses of rats made cataleptic with the dopamine antagonist haloperidol. Vestibular and auditory stimuli released catalepsy sequentially from the shoulder, forepaw, body center, hip, and hind paw. Familiarity with the sound cue increased the movement size of release from catalepsy and improved the temporal coupling of trunk and limb movements to normalize the righting movement. Thus, the present study established a method for evaluating sensory-induced behavioural activation in normal and dopamine-comprised rats that can be further used to investigate the neural basis of sound-induced activation.

Previous work using the "jump task" demonstrated that catalepsy could be overcome by postural instability (Morrissey et al., 1989; Field, Whishaw, and Pellis, 2000). Cataleptic rats placed on an inclined plane exhibit an all-or-none jump to regain equilibrium at an angle of incline that otherwise would have caused them to topple. This finding suggested that the allied reflexes associated with the postural support of catalepsy were activated to restore postural equilibrium. Using a new method to induce postural instability, rats were placed on a wire mesh cage with a forelimb and a hind limb suspended over one edge. When the cage was slowly tilted, the animals made a righting response to counteract the tilt. A measure of the tilt angle of the cage in relation to the rats' response gave an objective measure of the displacement required to produce righting. At successively larger tilt angles the rats first shifted the head, followed by the forelimb, and then the hind limb. Thus, the results not only confirm a relationship

between postural displacement and righting, they provide a way obtaining a graded and sensitive relationship between postural displacement and righting (Golani et al., 1981; Teitelbaum, Schallert, and Whishaw, 1983).

Although body size complicates the measure of righting in catalepsy (Sanberg, Ossenkopp, and Kavaliers, 1996), it is unlikely to affect the present results because the cage supports the rat's body throughout the test. Sex differences have also been reported to affect the righting response of cataleptic rats. The present model could be used to further investigate such differences. Relating the amount of physical destabilization to stages of the righting movement allows for a sensitive comparison of righting responses between males and females. For example, although males and females both brace against a displacing force during the jumping task, they do so using different strategies (Field, Whishaw, and Pellis, 2000). Females have a bias to use their forelimbs for support on the tilting plane, whereas males lean back onto their hind limbs. Thus, the present method could be used to document the relationship between postural instability and differences in postural righting in haloperidol catalepsy, independent of sex and body size.

The present study also demonstrated that a familiar auditory cue of key jingling could release rats from catalepsy. Classical studies on cataleptic akinesia reported that sensory cues such as tail pinch or eye and neck bandaging could produce release from cataleptic clinging in adult rats with catecholamine depletion or lateral hypothalamic lesions, as well in intact infant rats (Teitelbaum et al., 1976; Teitelbaum, Schallert, and Whishaw, 1983). The present study is the first to use sound to activate postural support mechanisms in the cataleptic rat. Previous work demonstrated that sounds produced from the crinkling of a chip bag could helps rats to overcome a spatial deficit (Whishaw,

1993), however pilot observations using the current model indicated that sounds produced by key jingling were more effective at eliciting righting than those produced by crumpling a chip bag. Key jingling produces a sound that roughly includes frequencies of 200 Hz to 75 kHz, thus covering the rat's entire hearing range, and has a sharp onset with distributed power spectra at many frequencies. Key jingle behaviourally activates rats, to the point of inducing audiogenic seizures in seizure-susceptible rats if presented for an extended period (Barto, 1956; Falk, Somson, and Winger, 1972). The potent effect of key jingling on rat behavior was the reason that the stimulus was included in the present study, although it is important to note its presentation was brief and did not evoke seizures.

The way in which the animals responded to vestibular displacement and auditory stimulation was different. Following vestibular cue onset, the forepaw flexed and extended, such that the paw remained suspended as the body resumed a static posture. As the tilt angle increased, animals displayed lateral movements of the shoulder and head. Forepaw lift and placement was followed by intermittent movement arrest, additional adjustments of the shoulder and hip, and placement of the hind limb. Because the tilt stimulus continued until the animal placed both paws, or a 90 degree tilt angle, there was a longer latency between tilt onset and movement and a longer duration of time needed to complete righting. Conversely, familiar single and repeated auditory cues produced a quick, continuous, and complete movement in rats with auditory cue experience. It should be noted that multiple key jingles, analogous to that of an ongoing musical stimulus in PD patients, were not more potent than a single presentation of auditory cue at releasing experienced rats from catalepsy. Following presentation of key jingle, there

was pinna erection in the direction of the sound source followed by simultaneous movement of the shoulder and forepaw. As the forepaw was placed, the hindquarters rotated to match the anterior-posterior orientation of the front half of the body, and the hind paw flexed and was placed. Thus, the auditory cue produced a complete and "normal appearing" righting response versus the sequential response produced by the vestibular stimulus.

Experience with the vestibular and auditory cues further improved release from catalepsy. Experienced rats were provided with task experience for three days, whereas naïve rats were habituated to the apparatus without sound stimuli. Task experience consisted of six randomized stimulus presentations (three sound and three tilt) over five minutes. Offline analyses of tilt-induced righting responses revealed large movements and dual paw placement in rats with tilt experience. Rats without tilt experience often exhibited an absence of rotation or movement in the hip following forepaw placement, which was associated with the rat clinging vertically to the grid with the forepaws at a maximum angle of tilt. Experience with the auditory cue increased the likelihood of release from catalepsy following sound. Rats without prior sound experience were less likely to respond with righting and exhibited smaller movements of the shoulder and hip. Rats that were pre-trained with the jingling key stimulus and tested with the key stimulus exhibited the largest righting responses. Conversely, rats that were experienced with keys or the crinkling chip bag but tested with chip bag performed poorly.

Our data are consistent with the literature indicating that familiar auditory stimuli (i.e., music) can release Parkinson's patients from akinesia (Sacks, 1973). A recent case study revealed a therapeutic effect of familiar music, such that a severe dyskinesia was

absent while a patient listened to a preferred song (Sacrey, Clark, and Whishaw, in preparation). Although familiarity with musical pieces or songs is often established prior to disease, the impact of training is also evident (Thaut et al., 1996). In humans, activities of daily living such as gait often occur in the presence of music, and patients studied in our laboratory report that music has a relaxing effect and makes household tasks easier to perform (Sacrey, Clark, and Whishaw, in preparation). As PD progresses, sound remains an external cue that can release people from muscular rigidity and catalepsy (Sacks, 1973) and produce "paradoxical kinesis" (Dibble et al., 2003; Ballanger et al., 2006). Correspondingly, animals displaying pharmacologically induced catalepsy also display paradoxical kinesis in the presence of external stimulation (Cenci, Whishaw, and Schallert, 2002). The present model is similar to the human situation in that sounds that are best at activating movement are often related to movement prior to changes in dopamine transmission. Recent studies suggest that paradoxical kinesis is not unique to PD and is an attribute of the motor system, as external cues and urgent conditions reduce movement durations in identical amounts in PD patients and healthy controls during a signal detection task (Ballanger et al., 2006). Future work using this model could make use of alternative training paradigms to investigate learning contexts and composite movements (versus a single release from catalepsy in the form of a righting reflex), and vary acoustic features of the stimuli to identify neural correlates of elicited paradoxical movement.

There are a few possible mechanisms underlying the neural basis of the sound-induced release of catalepsy. First, sound-induced activation of the motor system may be due to auditory cues acting on intrinsic auditory-motor connections that are sensitive to

external stimulation, and thus mediated by classical auditory regions. Recent studies suggest the role of music in providing a temporal template to which motor systems at multiple levels (Thaut, 2005), and the influence of auditory cues on prompting species specific behaviour in rodents is clear (Wöhr and Schwarting, 2007). A recent study by Lahav (2007) highlights audiomotor mirror neuron networks in the primate brain that are activate in musicians while listening to well-learned musical pieces. Second, acoustic stimuli may promote behavioural activation via a module that is dedicated to behavioural activation. A number of studies highlight pathways that amplify behaviourally relevant signals and provide a mechanism for sound-induced activation beyond classical auditory areas (Anderson et al., 2006; Mooney et al., 2003). The increasing amount of evidence for a neural architecture that synchronizes remote structures provides a source for future investigation.

In conclusion, the present study demonstrated a rat model of music-induced behavioural activation. This new method allows for comparison of righting responses induced by auditory cues and controlled vestibular displacement. Familiar sound was found to be more potent for releasing catalepsy than novel sound at eliciting movement.

CHAPTER FOUR

ACTIVATION FROM CATALEPSY WITH FAMILIAR ULTRASONIC VOCALIZATIONS OR SINGLE FREQUENCIES: CONSTRAINTS ON SOUND-INDUCED MOVEMENT IN THE PARKINSONIAN RAT

ABSTRACT

Externally driven conditions, such as vestibular stimulation or familiar music, are able to release Parkinson's disease patients from catalepsy. However, while the neural basis of vestibular-based improvements has been characterized, the mechanism of music-induced improvements remains unclear and cannot be studied in the human subject, so we turn to the rat model. Adult male Long-Evans rats were filmed for postural responses following a familiar or unfamiliar auditory cue (key jingle) or physical displacement (control tilt) after single acute administration of 5 mg/kg doses of saline or the neuroleptic, haloperidol, to model parkinsonian muscular rigidity. Movement notation was used to describe the qualitative components of the righting response. Results showed that the auditory cue was able to temporarily release rats from catalepsy and was better at normalizing the temporal coupling of trunk and limb movements than the tilt control. Further, the familiar sound cue increased the probability of release from catalepsy, indicating this is a valid model of music-induced improvement seen in human Parkinson's disease.

INTRODUCTION

As a movement disorder, Parkinson's disease affects an individual's ability to respond appropriately to ongoing and novel environmental stimuli in order to trigger and guide movement. Although pharmacologic treatments are widely used, chronic use is associated with debilitating motor deficits. Difficulties in performing daily activities in those with movement disorders, including Parkinson's disease (PD), can be improved with physical therapy. In the previous chapter of this thesis, discrete auditory cues that have previously been paired with movement were used during transient dopamine depletion to release rats from experimental catalepsy. In this way, auditory stimuli can be used to supplement motor learning (Ma et al., 2004; Thaut et al., 2001), modeling task-specific physical therapy, and elicit spontaneous movement during a grid climbing task from rats exhibiting haloperidol-induced catalepsy, a model of advanced parkinsonism. In rats, sounds broadly associated with specific frequencies, such as 22- and 55-kHz, have been shown to influence rat vocalization (USV), approach or startle behaviour, and social behaviour (Sadananda, Wöhr, and Schwarting, 2008; Wöhr and Schwarting, 2007; Brudzynski and Chiu, 1995). Infant primates also produce calls to release appropriate parenting behaviour (Geiss and Schrader, 1996). Previously, release from catalepsy following a control vestibular stimulus (Field, Whishaw, Pellis, 2000) was compared with release induced by key jingle and crinkling chip bag. Further, rats with prior motor experience to key jingle performed better than naïve or chip bag trained rats. A review of the human literature on auditory cueing in PD highlights the contribution of stimulus type (i.e., physical versus music therapies) (Rubinstein, Giladi, and Hausorff, 2002), previous

auditory-motor experience (Sacks, 1972; Thaut et al., 1996), and the specific auditory cue used (Thaut, Rathbun, and Miller, 1997).

Although our laboratory has documented the potency of familiar key jingle for releasing rats from catalepsy, the effectiveness of more behaviourally relevant auditory stimuli is unclear. To clarify the underlying mechanisms of sound-induced improvement, it is important to understand if dedicated neural networks exist to increase arousal and activation in a rat following species-specific sounds, or if areas within classical auditory regions share this function. Because infant and adult rats emit well-characterized ultrasonic vocalizations (Wöhr and Schwarting, 2007), the current study aimed to investigate the effect of experience on righting in cataleptic rats following relevant frequencies, and USV.

In the present study, normal rats were given three days of task experience, consisting of six randomized stimulus presentations (three sound and three tilt) over five minutes, or habituation (in the absence of stimuli) to a grid box apparatus. Male rats were then administered haloperidol, a dopamine antagonist, on the following day to produce experimental catalepsy. Movement notation analysis was conducted offline to document righting components following vestibular and auditory stimuli. Analyses revealed that rats with experience in responding to USV performed slightly better than naïve rats. Surprisingly, experience with 55 kHz frequency significantly decreased performance in cataleptic rats.

MATERIALS AND METHODS

Subjects

Twenty-six male Long-Evans Hooded rats, approximately 6 months old at testing, were obtained from the University of Lethbridge colony where they were housed in pairs in Plexiglas® cages and kept on a 12:12 LD cycle (with dark phase beginning at 7:30pm) with ad libitum access to food and water. Prior to testing each rat received about 3 min of handling in the colony room for one week and 3 min of handling in the test room for one additional day. Handling consisted of picking up the rat from its cage and replacing it a number of times. Testing was carried out during the light cycle. Experiments were conducted in compliance with the guidelines of the University of Lethbridge animal care committee and the Canadian Council on Animal Care, which complies with international standards for animal care.

Drug

Drug dosage of 5mg/kg of Haloperidol (Sigma-Aldrich) was administered intraperitoneally 20 minutes prior to the righting trials. Saline controls in experiment one received an equivalent volume of physiological saline. Drug controls received equivalent volumes of haloperidol. Injections were given during the testing session.

Apparatus

The grid box apparatus consisted of a rectangular metal grid cage (30cm x 65cm x 15cm) secured to a Plexiglas® base (Figure 4.1, top). The grid box could be manually

tilted by a lever (20 cm in length) attached to the left side of the cage. A protractor was used to verify tilt speed. The apparatus was placed on the edge of a one-meter high table and could freely tilt away from the edge of the table over a padded elevated surface.

Figure 4.1. Cataleptic rat in testing position on grid box apparatus.

Video Recording

Rats were video-recorded (30 fr/s) laterally for stimuli-induced movements during testing. Video-recordings of the lateral view of the rat were used for offline frame-by-frame analysis.

Group Assignment

Rats were assigned to six groups: 1) saline control; 2) drug control; 3) naïve to ultrasonic vocalization; 4) experienced with ultrasonic vocalization; 5) naïve to ultrasonic frequency, and; 6) experienced with ultrasonic frequency.

Saline and drug controls were given three 3-minute habituation sessions on consecutive days. "Naïve" rats were also given three habituation sessions. Habituation sessions consisted of having each rat walk on the surface of the grid box for three in the absence of vestibular or auditory stimuli. Experienced rats received three 3-minute "training" sessions during which they were prompted to climb the grid box in response to three tilt and three sound presentations (vocalization or frequency, according to group assignment).

Evaluation of catalepsy

Catalepsy was determined by the latency to initiate movement of the limbs or trunk away from the start position (minimum criteria was 30 seconds, to a possible maximum of 60 seconds). Using a minimum 30-second latency, normal rats do not display catalepsy (Kuschinsky and Hornykiewicz, 1972). Rats were placed on the grid box with one forelimb and the ipsilateral hind limb suspended over the vertical wall of

the cage, with the nose placed at a 45° angle to the body to produce slight curvature of the trunk (testing position) (Figure 4.1). If a haloperidol-treated rat immediately turned away from the side of the cage and brought both ipsilateral paws to the grid surface, or if they exhibited a low intensity of muscular rigidity (evaluated qualitatively), the animal was returned to a transfer cage for an additional three minutes before subsequent testing, and this was repeated until catalepsy was reached. Righting trials began after catalepsy evaluation.

Sensory stimuli

For the righting response testing session, saline and drug controls were not presented with any sensory cues during ten trials. Based on previous work, it was expected that saline-treated rats would right immediately and climb the grid, whereas haloperidol-treated rats would maintain the position they were placed in. Rats were randomly presented with five tilt and five sound trials.

(1) Vestibular stimulus

For the vestibular stimulus, the grid box tilted at a rate of 2° per second to a maximum of 40 degrees or until the rat righted by brining all four feet to the horizontal surface of the grid. Tilt of the grid box at 2° per second was time-synched with a clock. If a trial provided vestibular displacement greater than 2° per second, the trial was discarded.

(2) Auditory stimuli

Because sounds within the "50 kHz" range have been associated with approach behaviour (i.e., motor activation) (Wöhr and Schwarting, 2007; Brudzynski and Pniak,

2002) and are ethologically relevant to the rat, a 55 kHz frequency was used for the grid-climbing task (audio set up included HP 8903B Audio Analyzer, Alesis RA150 2-channel Amplifier, Monitor Audio Loudspeaker, muRata Manufacturing Co Ltd Tweeter System ES105, and LabView, National Instruments). A recording of USV produced by males calling for a female setting were played back at 75dBc through Windows Media Player.

Quantification of Righting

The righting response was measured by noting the body movement made to regain posture on the vertical surface of the grid box in relation to time of the response. From the video record the time at which a rat initiated and completed a Hip, Shoulder, Hind Paw, Forepaw, Head movement was recorded and notated on a time-line chart (Fig. 4.3). For quantification the individual movements were labeled from 1-5, with 1 being a head movement and a 5 being a complete righting response.
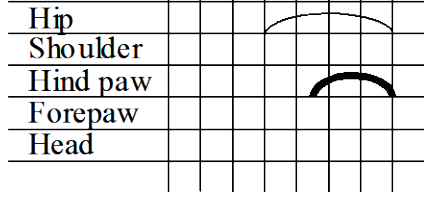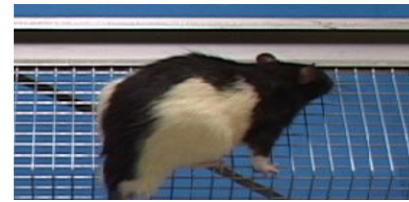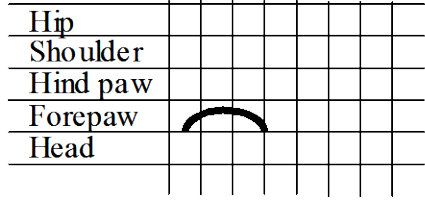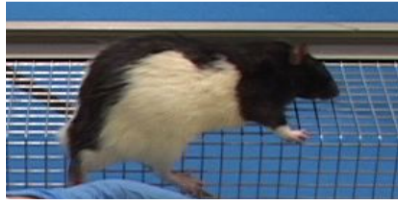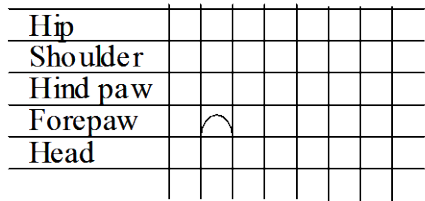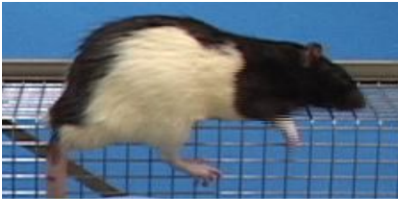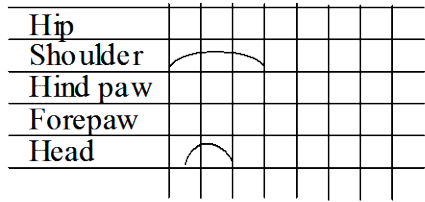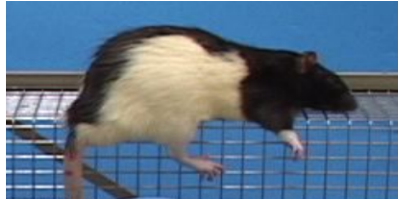
Figure 4.2. Measurement scores for five cephalocaudal components. Left: Photos illustrate the final position of movements of the Head, Forepaw, Hind paw, Shoulder, and Hip. Right: Score of righting response components. Vertical bars represent units of time (milliseconds). The arcs represent duration of movement.

Experimental Procedure

Rats in all groups were handled three minutes daily for one week, which consisted of holding and replacing the rat in its cage. During habituation trials for saline controls, drug controls, and naïve groups, rats were given three minutes daily for three days to explore the horizontal surface of the grid box in the absence of tilt or auditory cues. Experienced groups explored and climbed the grid box apparatus with three random vestibular and three random auditory cue presentations. "Stimulus" groups were then tested under drug with cues that were then familiar or novel. Controls were tested under saline or drug without cues.

Statistical Analysis

Statistical analysis was performed using SPSS (version 13). Repeated measures analysis of variance was conducted to test for the effects of group and stimulus type on righting size. Post hoc analysis used Least Significant Difference with a p value of less than .05 was the criterion for statistical significance.

RESULTS

Movement Notation

Movement notation analysis revealed differences in the righting responses elicited by the vestibular and auditory stimuli (Figures 4.3 through 4.5). When placed on the grid box, saline-treated rats replaced all limbs on the grid surface immediately following placement. Drug-treated controls rarely exhibited righting within 20 seconds of the

researcher removing his or her hands from the rat after placement on the grid. Vestibular-induced responses were longer in duration and characterized by discrete movements of the Head, Shoulder, Forelimb, Hip, and Hind limb. Righting responses prompted by a familiar 55-kHz presentation were able to prompt a quick forepaw placement, but did not bring about a full righting of the body. Ultrasonic vocalization did not reliably elicit movement in experienced or naïve rats.
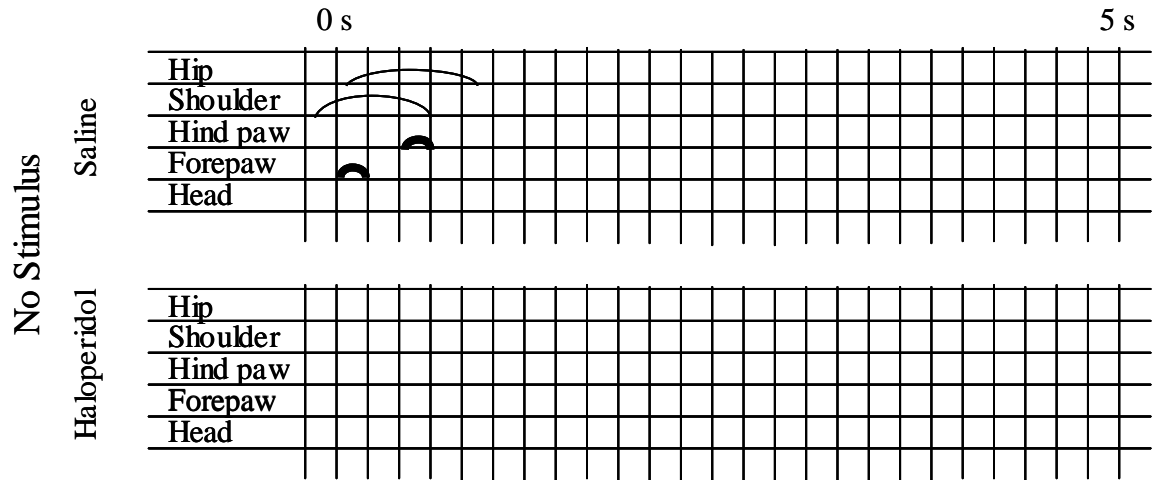
Figure 4.3. Movement notation results for drug effect. Saline-treated rats immediately righted, whereas cataleptic rats did not display release from catalepsy in the absence of sensory cues.
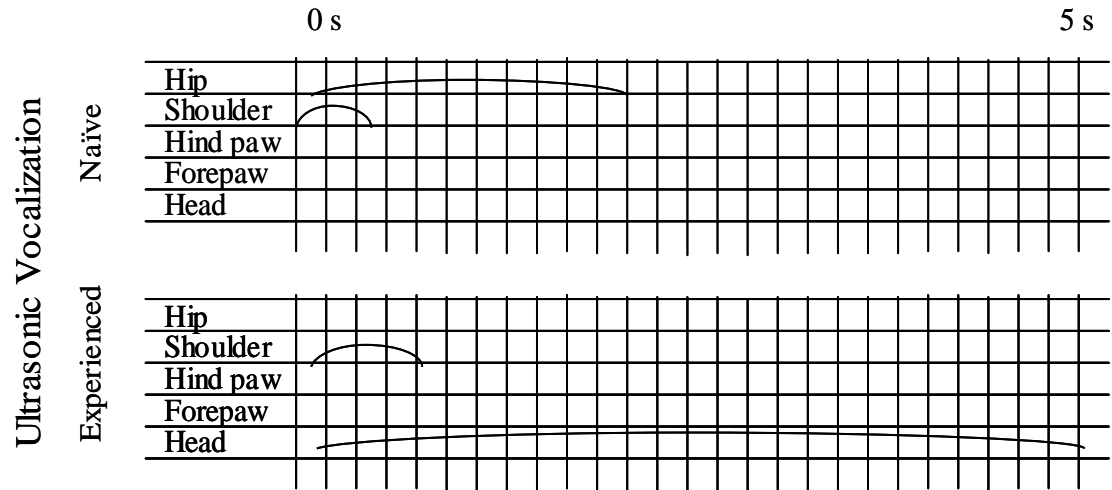
Figure 4.4. Movement notation results for USV. Naïve rats exhibited brief sway of the trunk. Rats with USV experience displayed lateral sway of the shoulder away from the edge of the grid box and a lowering of the head.
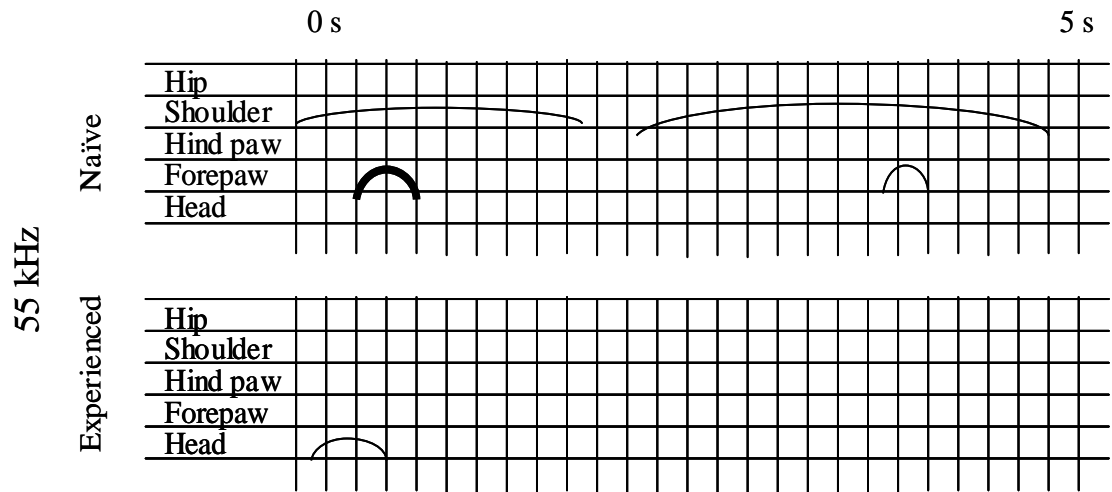
Figure 4.5. Movement notation results for 55 kHz. Naïve rats displayed flexion or placement of the forepaw. Experience with the auditory cue reduced performance to lift of the head.

Size of Righting Response

Offline kinematic analyses indicated that vestibular and auditory cues prompted different degrees of cephalocaudal righting in haloperidol-treated rats. It is important to note that during the three days of training to the auditory cue, the untreated rats displayed increasing orientation of the body to the sound source, locomotion, and approach toward the sound while on the grid apparatus. That is, they each appeared to be activating to normal rats and increase movement. During the testing session, saline-treated rats immediately righted whereas cataleptic rats did not right in the absence of sensory stimuli. These levels of performance are illustrated by the dotted lines in Figure 4.7. A complete righting response consisted of rotation and lift of the shoulder and forepaw, followed by the hindquarters. Naïve and experienced rats exhibited incomplete or absent righting in response to auditory cues.

There was a significant effect of Group on the size of righting responses, $F(5,48)=78.326$, $p<.001$. There was also a significant effect of Stimulus on the size of righting, $F(1,48)=317.926$, $p<.001$. The interaction between Group and Stimulus was significant, $F(5,48)=47.306$, $p<.001$. In contrast to previous experiments using the grid box task, familiarity with the USV auditory cue produced a non-significant improvement in release from catalepsy from naïve rats. There was an unexpected effect of training on righting following 55 kHz; motor experience significantly decreased response under catalepsy. Following presentation of auditory cues, pricking up of the pinna was observed, but treated animals did not display a cephalocaudal righting response.
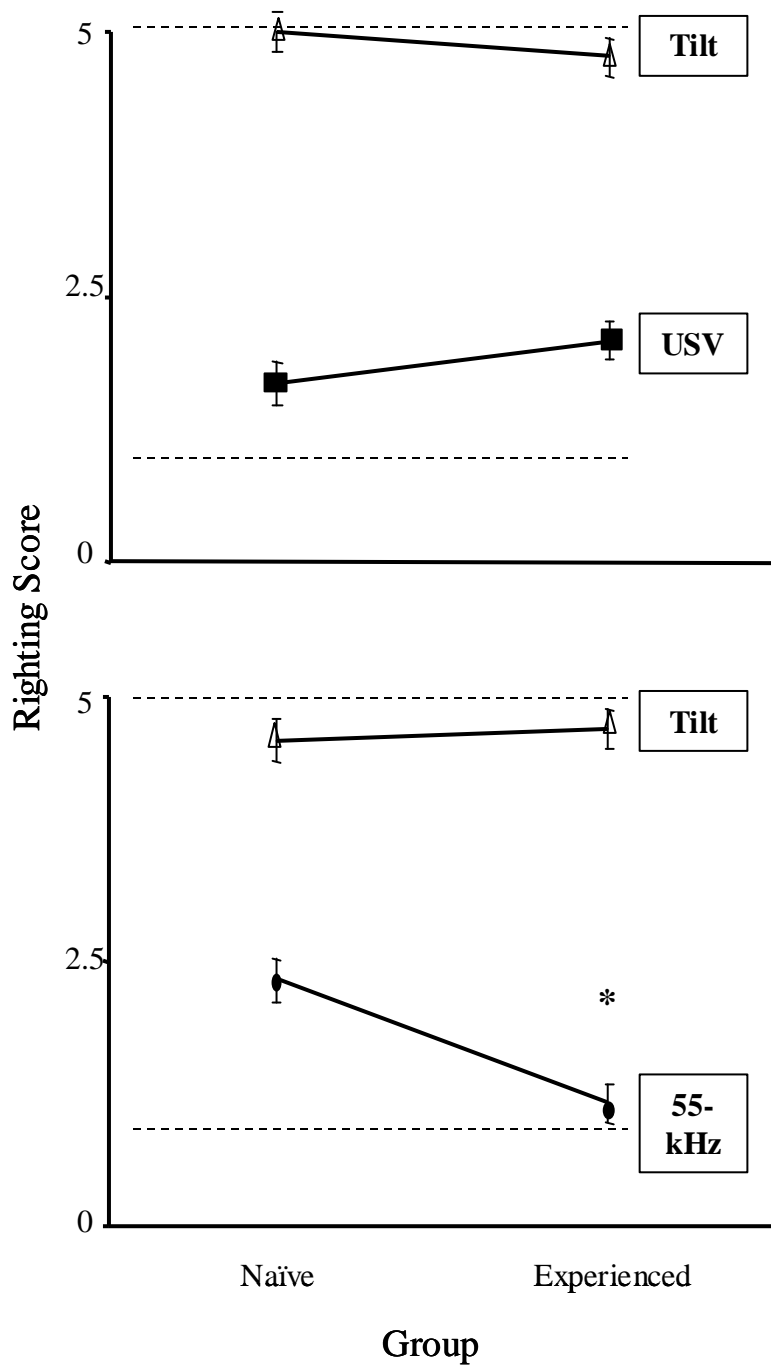
Fig 4.6. Righting size for 55 kHz and USV. The vestibular stimulus prompted complete righting responses, whereas both auditory stimuli were not able to reach control stimulus levels. The △ symbol denotes tilt trials. The ● symbol denotes 55-kHz trials. The

■ symbol denotes USV trials. (* indicates p<0.05). The upper and lower dotted lines show performance of saline and drug controls, respectively.

DISCUSSION

The present study demonstrated that motor experience with ethologically relevant auditory cues did not improve performance of rats during a righting task. The control vestibular stimulus was able to release rats from catalepsy in a cephalocaudal manner. Although previous experience with tilt does not significantly change performance on the grid box task using this cephalocaudal scoring method, experience does influence auditory-induced righting. By using ethologically relevant sound stimuli, this experiment complements previous research on sound-induced activation and showed that not all sounds are influenced in the same way by experience and drug treatment.

Our hypothesis that rat USV would act as a salient auditory cue for activation, and that training would further increase this potency, was not supported by the current data. The strong influence of USV on releasing species-specific behaviour in rodents can be seen in one study that systematically varied the onset of dominant frequency in pup calls (Geissler and Ehret, 2001). In fact, results showed that caring behaviour was no longer released when the frequency components of infant calls were changed. Although we did not vary "formants" of the USV call used, haloperidol rats were unable to express righting in the presence of a normally potent USV call. It is possible that the rats did not respond with complete righting responses to the USV because it was recorded from males calling in the presence of estrous females. Future work could present female calls, or present olfactory cues with the auditory stimulus.

Although it has been shown that normal rats show approach, and we could argue "activation" behaviour, in response to "50 kHz" USV playback (Wöhr and Schwarting,

2007), the potency of this single frequency was blunted under haloperidol. In fact, both the single frequency and USV seemed to be salient auditory stimuli during training sessions without drug. Despite the fact the current study did not make use of a more complex frequency stimulus (with more than one frequency generated), we have shown that response to frequencies important to the rat have a different effect in haloperidol-treated rats.

Experience with the 55 kHz cue decreased release from catalepsy in the rat. Previously, we found that experience only improved sound-induced righting components during grid climbing when tested with the same auditory stimulus. There are three possibilities for this phenomenon: 1) training to the 55 kHz tone produced habituation that continued under DA depletion; 2) the training session itself, along with the tilt stimulus, served to reinforce prolonged arousal during training, and not the 55 kHz tone, and; 3) because decreased dopaminergic striatal tone is associated with sensory changes (Rascol et al., 2002), haloperidol-treated rats may require louder sounds, or those that contain a wider frequency band, to initiate movement. The first possibility cannot be excluded, although the researcher did not observe any overt diminished response to the frequency during training sessions. The second possibility is not likely, because: 1) normal rats show large orienting reflexes to 55 kHz tone, and: 2) during habituation trials without stimuli, untreated rats exhibit locomotion on the horizontal grid surface, but do show a slowing of movement near the end of the third habituation session, whereas rats trained to 55 kHz or USV do not. This observation would support the idea that the tilt and/or sound stimulus is prolonging the locomotion and activation observed during training sessions with cues. The current data cannot speak to the third possibility, but it

remains a possibility, as key jingle, known to produce audiogenic seizures when presented for a time (e.g., Barto, 1956), is made up of a strong power spectrum across the rat hearing range. Lastly, future work using this task could examine the contribution of context. A number of "home cage phenomena" exist in the DA literature in addiction and operant conditioning studies (Robinson and Berridge, 2003; Berke and Hyman, 2000). Our own observations showed that catalepsy temporarily disappeared when haloperidol-treated rats were returned to the home cage, their cage mate, or a familiar smelling transfer cage.

Our findings indicated that rat vocalization and a frequency associated with reward and pleasure in the rat were not as effective as the key jingle stimulus (as presented previously in this thesis) are consistent with anecdotal and clinical research showing that not all music affects movement deficits of PD patients in the same way (Sacks, 1973; Sacrey, Clark, and Whishaw, in preparation). For example, the classical case studies of patients "awakened" from parkinsonism by levodopa treatment could also be helped by auditory stimulation, although heavily percussive sounds could cause patients to move in a fragmented manner (Sacks, 1973). Thus, a patient's own experiences, in addition to the frequencies, power spectra, and gestalt of the auditory cue should be considered when designing a music therapy program.

In conclusion, the current grid-climbing task provides a simple paradigm that can be used to investigate sensory manipulations on parkinsonian akinesia and the neural basis of music-induced improvements.

CHAPTER FIVE

DISCUSSION

DISCUSSION

Hypothesis One: Sound-induced Activation in the Normal Rat

Our first study examined the orienting responses of saline- and haloperidol-treated rats while in a quiet resting state. We observed a characteristic three-stage orient following sounds that were most activating, including key jingle, crinkling chip bag, ultrasonic vocalization. The presence of Orient, Attend, and Disengage phases were absent in haloperidol-treated rats, a finding consistent with studies suggesting that syntactic grooming chains are often incomplete in rats with striatal damage (Whishaw and Berridge, 1992). We did not find a cephalocaudal orient to sound frequencies, or that specific frequencies evoked larger responses. Cataleptic rats treated with haloperidol were more responsive to auditory stimuli comprised of multiple frequencies with complex timbre. These findings support the theory that the intact BG acts to maintain the expression of motor chains through internal cueing.

The current research made use of a cephalocaudal score that was applied during both the orienting and righting tasks. A cephalocaudal principle of motor recovery can be seen in infant rats as they explore their surroundings and also in recovery following LH€ lesions (Golani et al., 1981; Teitelbaum, Schallert, and Whishaw, 1983). Lesions to the hypothalamus can also produce a period of acute catalepsy before eating and locomotion resume (Golani et al., 1981; Teitelbaum, Schallert, and Whishaw, 1983). Additionally, cephalocaudal recovery can be seen during haloperidol-induced catalepsy, as documented in the current experiments. By applying a cephalocaudal scale to the responses observed, we gained insight not only into the presence or absence of movement, but could

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demonstrate subtle differences in movement that would otherwise be missed by temporal measures of orienting or righting alone. To complement the cephalocaudal five-point score used in this thesis, a modified Eshkol-Wachman Movement Notation (EWMN; Eshkol and Wachman, 1958) score was used to describe movement components during orienting and righting tasks. Of special interest is the assigning of "heavy" and "light" limbs in EWMN. The orienting and righting responses, in particular, used in this thesis were adaptable to an EWMN-like movement analysis system, as the elicited cephalocaudal movements were characterized by lateral rotation at the shoulder or hip and followed by independent movements of the lighter limbs.

The current study differentiated movement associated with the acoustic startle response from that of sound-induced orienting and release from catalepsy. The acoustic startle reflex relies on low-level auditory processing and alerts the animal to an impending object within the environment (Sokolov, 1963). Conversely, the neural and motor responses to key jingle, for example, are more robust and complex. At the level of the inferior and superior colliculi, sensorimotor integration allows for a directed behaviour to localize a stimulus. Additionally, the activating stimuli used in the current study can be thought of as providing sensory stimulation in place of proprioception that allows for automatic behaviours to be released. It is possible that the motor experience given during the grid-climbing training reinforced cortical areas to respond with motor activation to salient auditory cues within the grid-box task. Thus, we postulate that we are looking at two different behaviours, one characterized by simple spinal reflexes, and the other characterized by the postural, proprioceptive, and auditory guidance of movement.

Hypothesis Two: Sound-induced Release from Catalepsy

Catalepsy, a model of PD akinesia in which there is an absence of spontaneous or voluntary movement, can be produced experimentally in the animal by the administration of opiates or classical neuroleptics. Further, morphine- and haloperidol-induced catalepsy produce different forms of akinesia/catalepsy (De Ryck, Schallert, and Teitelbaum, 1980). Conversely, haloperidol rats will remain immobile until physical destabilization elicits a brief jump (Teitelbaum, Schallert, and Whishaw, 1983; De Ryck, Schallert, and Teitelbaum, 1980); postural mechanisms responsible for static support are left intact. In addition to vestibular stimuli, sensory stimuli including heat and neck bandaging temporarily release animals from catalepsy (Teitelbaum et al., 1976; Teitelbaum, Schallert, and Whishaw, 1983). Haloperidol was chosen for this series of experiments because it provides an established model of parkinsonism that allows for collection of data on isolated postural systems and associated subsystems.

There is a large literature on neuroleptic-induced catalepsy. Previously, experimental catalepsy was measured in terms of latency to move from an imposed posture. Haloperidol-induced catalepsy is a behavioural state in which postural support systems remain active, to provide static equilibrium for the animal. Correspondingly, rats displaying haloperidol-induced may exhibit spontaneous release after a period of time, or movement if the allied reflexes for postural support are activated through physical displacement. Established paradigms to test spontaneous or induced release from catalepsy included the classical "bar test" and the "jump task." First, the bar test consists of placing the rat's forepaws upon a raised block that may be varied according to body

size of the rat (Kuschinsky and Hornykiewicz, 1972). Sanberg, Ossenkopp, and Kavaliers (1996) note that handling can significantly influence sensitization to catalepsy by activating the immobility reflex with pressure at the nape. Second, the jump task involves placing a rat on a textured surface that can slowly be tilted along the anterior-posterior plane of the rat, to produce an all-or-none jump (i.e., "release from catalepsy"). When the rat is no longer able to brace against the increasing displacement, postural reflexes prompt a quick jump. The rat then resumes immobility once landed (Field, Whishaw, and Pellis, 2000). The present experiments provided a modified version of the jump task in which lateral tilt of the animal revealed cephalocaudal righting, made possible by an apparatus that supports the entire body of the animal. The current research is the first to document a graded release from haloperidol-induced catalepsy. Future work could compare the amount of displacement needed to prompt righting in the current grid-climbing task with the angle of tilt needed to elicit a jump during the jump task (Field, Whishaw, and Pellis, 2000).

We developed a modified version of the jump task that could be used to show graded vestibular- and auditory-induced release from catalepsy. Correlation analysis of vestibular- and auditory-induced righting indicated that movements prompted by key jingle were more "normal" appearing than those produced by the vestibular stimulus; the sound stimulus produced a continuous movement that was not dependent on a progressive physical stimulus. Second, movement notation analysis indicated that multiple brief presentations of key jingle (perhaps more analogous to a prolonged musical stimulus) were not more effective than a single key jingle for release from catalepsy. Third, our grid box experiments revealed that certain sounds are more effective for

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eliciting righting responses in haloperidol-treated rats. Namely, the key jingle was more effective than ultrasonic vocalization and sounds produced by a crumpling chip bag. The 55-kHz frequency was least effective during the righting task. Thus, this research demonstrates that central mechanisms responsible for paradoxical movement in parkinsonism respond preferentially to complex sound stimuli.

Hypothesis Three: Effect of Experience on Sound-induced Release from Catalepsy

We aimed to investigate the contribution of cued grid box experience on release from catalepsy. As noted, multiple presentations of key jingle stimulus were not more effective than a single presentation, and previous experience improved only the righting induced by the single key jingle stimulus. A second experiment indicated that rats trained and tested with chip bag righted with smaller movements than those trained and tested with key jingle. Conversely, rats trained with crumpling chip bag sounds but then tested with key jingle performed at levels equivalent to rats trained and tested with key jingle. Rats naïve to key jingle righted with smaller movements than rats pre-trained with chip bag sounds. Therefore, grid-climbing experience with a less potent sound stimulus (i.e., chip bag) facilitated a level of activation that could be utilized for testing with a more effective auditory cue (i.e., key jingle). As well, rats that were familiar with the key jingle stimulus but tested with chip bag sounds performed worse than rats that were entirely naïve to the task. Release from catalepsy induced by the ultrasonic vocalization stimulus was not improved by experience, an observation that could be expanded on in future work. One surprising finding included diminished performance with experience following 55-kHz cued trials. Lastly, A sex difference was found when key jingle was

used to induce righting. Specifically, the performance of females did not reach male performance levels and training did not improve righting during the task, despite no group differences in naïve animals. It is suggested that estrogen is neuroprotective, as estrogen replacement therapy serves as a treatment for early PD (Leranth et al., 2000; Saunders-Pullman et al., 1999). As well, estrogen serves to increase DAergic tone (McDermott, Liu, and Dluzen, 1994).

"Paradoxical kinesis" in haloperidol rats has previously been demonstrated in experiments using physical displacement, changes in temperature, tail pinch, and neck bandaging (Whishaw, Mittleman, and Evenden, 1989). The current findings suggest that the movement systems left active during DAergic blockade function to protect not only static stance and respond to defensive stimuli but also to regulate safety and arousal. As noted by Miklyaeva, Martens, and Whishaw (1995), rats with unilateral 6-OHDA lesions show deficits of the contralateral limbs that are likely due to an impaired ability to apply sufficient force to propel the body. Correspondingly, reflexes that are active during parkinsonian catalepsy may be a compensatory mechanism for movement initiation and due to external triggers or templates for movement. In addition, the demonstration that sensory stimuli other than vestibular displacement alone are able to elicit movement in the cataleptic rat suggest that PD akinesia functions to do more than preserve static equilibrium alone. Thus, dedicated neural systems might exist that are resistant to dopaminergic depletion and function to activate the animal in response to salient, well-trained environmental cues. Experimental factors such as previous drug administration, handling, and movements made while under haloperidol, can influence the expression of catalepsy (Sanberg, Ossenkopp, and Kavaliers, 1980).

A related aim of this research was to address the question, "What is the most potent sound for inducing movement in the normal and parkinsonian rat?" Results from our orienting and righting experiments revealed six main findings. First, normal rats do not respond with an equivalent orienting response and change in behavioural arousal to all frequencies within their hearing range. Second, haloperidol-treated rats exhibit a smaller orienting response (both "detection" and "localization") to frequencies that were salient for normal rats. Third, the presentation of all salient sounds and frequencies used in this thesis to untreated rats while climbing a grid (i.e., during training sessions) appeared to prolong behavioural activation beyond that of animals not presented with sound stimuli. A general observation that could be explored in future work is the finding that sound has the ability to bring about behavioural arousal that otherwise would not be present. For example, once in a quiet resting state in the orienting chamber, we found that rats left untouched would fall asleep, whereas rats given auditory stimuli would become alert and exhibit walking and rearing for a period of time. Fourth, a single key jingle was sufficient to prompt a quick righting response in haloperidol-treated animals naïve or familiar with the task. The potency of key jingle for righting, as well as for audiogenic seizures, highlights the ability of this stimulus to induce widespread, synchronous activity within the central nervous system. Fifth, sound stimuli or frequency bands that may be important for social communication were not potent enough to release haloperidol-treated from catalepsy during a righting task. Sixth, females did not improve their righting performance beyond naïve levels when given motor experience, providing an observation for future study. Although it was expected that females might respond more strongly to activating sounds, as it is the females who respond to the attracting calls of males, this

was not the case. Taken together, these six observations provide a starting point for future research into sound-induced movement in the rat, and also suggest that an "intrinsically" activating cue that may not be directly relevant to a species may be potent enough to be used in acute motor recovery.

Revisiting Music Therapy

The processing of musical stimuli in the brain, and the performing of music serve as models of human cognition and memory (Thaut et al., 2001). Within the study of music and motor behaviour, it has been shown that auditory cues can be used as discrete cues or as entrainment stimuli that can influence movement over time (McIntosh et al., 1998; Thaut et al., 1996). Briefly, the present experiments are consistent with emerging approaches to neurologic music therapy that encourage in-depth and standardized clinical assessments prior to application of music or rhythmic stimulation programs (Thaut, 2005). Currently, a cognitive neuroscience model is proposed (Thaut et al., 1999) in which external rhythmic cues work through coupled oscillator mechanisms to entrain ongoing movement: 1) EMG patterns synchronize to the felt rhythm (underlying meter) within two phases of the auditory stimulus (Thaut, 2005); 2) this immediate synchronization is also seen in controls who do not lack the integrity of internal movement generation provided by the basal ganglia; 3) the coupled oscillatory model is economical in terms of movement speed, time, and energy (Thaut, 2005); and 4) work by Ballanger (2005) suggests that "paradoxical kinesis" may be a general property of the motor system and not tied to deficient basal ganglia. Ballanger (2005) demonstrated that controls and PD patients increased their reaction speed during a signal detection task

when provided with urgent or external cues. Thus, the body of literature on music-induced activation in movement disorders highlights the following possibilities for why certain music and auditory cues can improve movement in PD: 1) redirects attention to the task at hand; 2) acts to "prime" the motor cortex for movement and increase tonic activity; 3) activates the remaining connections of the striatum that play a role in movement initiation and force; 4) bypass deficient areas by various compensatory mechanisms (e.g., regulation of timing is a distributed function in the brain; Cunnington et al., 2005; Thaut, Rathbun, and Miller, 1997); or 5) provide a sensory cue that helps the brain to compensate for impaired voluntary movement and the proprioceptive guidance of movement (Escola et al., 2002), and thus provide an external timekeeper or "template" (Ma et al., 2004).

CONCLUSION

In conclusion, the current research demonstrated that rats exhibiting haloperidol catalepsy could be released from catalepsy with activating sound, that auditory-motor experience influences the expression of sound-induced movement, and that key jingle is the most potent sound for inducing movement in the rat. These findings challenge the contemporary understanding of parkinsonian akinesia and suggest that the postural support systems left intact constitute a compensatory mechanism that allows environmental stimuli to guide the release of movement.

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