2017

The effects of Risperidone on the vestibular system of healthy volunteers as assessed by dynamic computed posturography

https://hdl.handle.net/2144/23759

Boston University
THE EFFECTS OF RISPERIDONE ON THE VESTIBULAR SYSTEM OF
HEALTHY VOLUNTEERS AS ASSESSED BY DYNAMIC COMPUTED
POSTUROGRAPHY

By

JOHN CHARLES CACCAVIELLO

B.S., Northeastern University, 2013

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2017
Approved by

First Reader

Dr. Kevin Thomas, Ph.D.
Professor of Anatomy & Neurobiology

Second Reader

Dr. Mark Moss, Ph.D.
Chairman of Anatomy & Neurobiology
I would like to dedicate this thesis to my parents. They don’t usually follow my academic life or have a minute to minute update on my daily activities, but I hope that this piece of work will provide a snippet of the type of research that I am interested in and part of. Without their continued support, I wouldn’t be where I am today.
I would first like to acknowledge Dr. Kevin Thomas for accepting me into his lab for Human Neurobiology and taking me under his wing for this thesis process. In the interim of it all, I have had the honor to meet two amazing and brilliant human beings that have grown to be both my mentors and best friends. Without Chris Brooks, I probably wouldn’t be in Dr. Thomas’ lab. If I never expressed interest in human neurobiology to Chris at a department retreat, he would have never provided me with contact with Dr. Thomas. One can imagine the butterfly effect of never approaching Chris that day. Chris has also taught me the importance of the use of precision in language, to always approach things with an objective mind, and more information about clouds and astrophysics that I would ever care to know. I would also like to acknowledge Craig Detheridge who, without his continued support, my thesis would never have existed. As the coordinator of the Balance Master study, Craig put my step in the door in a lab that was completely new to me. He was also a huge mentor in terms of my statistical analysis, my results section, and in the proofreading process of this thesis. These are all amazing human beings that I am extremely grateful to have grown to know.
THE EFFECTS OF RISPERIDONE ON THE VESTIBULAR SYSTEM OF HEALTHY VOLUNTEERS AS ASSESSED BY DYNAMIC COMPUTED POSTUROGRAPHY

JOHN CHARLES CACCAVIELLO

ABSTRACT

The pharmacodynamic effects of Risperidone on the vestibular system were assessed via dynamic computed posturography in 12 healthy subjects (6 male). Subjects were administered 2 mg, orally, of Risperidone and assessed on the NeuroCom® Balance Master© system under varying conditions. The vestibular response was deductively quantified by first assessing balance with a static force plate and eyes closed (Condition 2), and then assessed on a dynamic force plate with eyes closed (Condition 5). On average, Condition 2 scores were 24.46 points higher than Condition 5 scores (95% CI [20.973, 27.957]). A Pearson correlation between scores in Condition 2 and 5 showed a significant, moderate positive correlation ($r = .487, p < .001$). A trend analysis showed the effect of time, post-dose, on equilibrium score to be linear in nature ($p < .001$). In conclusion, some, but not all, of the subjects involved in the study experienced diminished vestibular control after administration of Risperidone; this may be due to phenotypic differences or learning effects.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td>i</td>
</tr>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vi</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>METHODOLOGY</td>
<td>8</td>
</tr>
<tr>
<td>SUBJECTS</td>
<td>8</td>
</tr>
<tr>
<td>TREATMENT DESCRIPTION AND CONDITION OF EVALUATION</td>
<td>9</td>
</tr>
<tr>
<td>CLINICAL ASSESSMENT AND BALANCE MASTER ASSESSMENTS</td>
<td>10</td>
</tr>
<tr>
<td>SENSORY ORGANIZATION TEST</td>
<td>11</td>
</tr>
<tr>
<td>RISKS</td>
<td>13</td>
</tr>
</tbody>
</table>
RESULTS.........................................................................................................................14

DISCUSSION....................................................................................................................18

INTERPRETATION OF ABNORMAL EQUILIBRIUM SCORES........18

SENSORY EFFECTS...........................................................................................................19

RELEVANT NEUROANATOMY.........................................................................................21

EFFECTS OF ATYPICAL ANTISPICYHTICS.................................................................21

IMPROVEMENTS AND FUTURE STUDIES.................................................................22

REFERENCES.................................................................................................................23

CURRICULUM VITAE.......................................................................................................35
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paired T-test between Condition 2 and Condition 5 Scores, paired by subject</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Pearson Correlation between Condition 2 and Condition 5 Across all Time Points</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Multivariate Tests of Time and Condition</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Trend Analysis of Within-Subjects Contrasts</td>
<td>18</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sensory Organization Test Conditions.</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Mean Equilibrium Scores for Conditions 2 &amp; 5 Across Time</td>
<td>15</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

ADT .............................................................................................................................. Adaptation Test
AP ................................................................................................................................. Antero-Posterior
BU ............................................................................................................................... Boston University
COG ............................................................................................................................. Center of Gravity
COM ............................................................................................................................ Center of Mass
ECG ............................................................................................................................ Electrocardiogram
MANOVA .................................................................................................................. Multivariate Analysis of Variance
MCT ............................................................................................................................. Motor Control Test
SOT .............................................................................................................................. Sensory Organization Test
INTRODUCTION

Risperidone (RISPERDAL®) is an atypical antipsychotic, a second-generation neuroleptic drug, that has been implicated in the treatment of several psychotic disorders such as bipolar disorder and schizophrenia [1-3]. Specifically, Risperidone has a benzisoxazole chemical structure with robust dopamine-2 (D2), serotonin-2A (5HT2A), alpha-1, alpha-2, and histaminergic (H1) receptor antagonism and some histaminergic excitation [1-11]. The 5HT2A receptors have its highest concentrations in the cortex [3]. Additionally, its “atypical” classification is due to its lower susceptibility to promote extrapyramidal side effects (e.g. tremor and dyskinesia) [1, 3]. Linear increases of such symptoms have been shown with increasing dosage increments of Risperidone, with a peak dose time of around 6 hours, correlating with the most significant effect on vestibular response (in terms of balance assessment) [3]. A dose of 6mg per day has been shown to pose the minimal amount of risk of extrapyramidal symptoms for most patients [3]. Risperidone has an approximate half-life of 20-30 hours with effects on D2 and 5HT21 receptor antagonism in the mesolimbic dopamine pathway and cerebral cortex, via the mesocortical and nigrostriatal tracks, respectively [1-9]. In relation to this study, it’s important to note that Risperidone has been linked to high resting energy expenditure and total energy expenditure in the mouse model along with a reduction in locomotor activity [8].

To the author’s knowledge, there is no primary literature on the effect of Risperidone on the vestibular system, in the human primate or the Mammalia class in general. Balance control and postural stability provide a means in which the effects of
Risperidone on the vestibular system can be assessed. Postural stability is defined as the threshold that an individual is able to maintain his or her Center of Mass (COM) over a given base of support that incorporates the regulation of the oscillation of the body’s Center of Pressure (COP) [3, 12-15]. This involves coordination of feedback from visual, vestibular, and somatosensory systems, along with central nervous system processing and musculoskeletal responses [3, 12, 13, 16-18]. Thus, technologies that detect center of pressure displacement are able to provide information on balance [3, 13].

Past postural studies have focused on falls in the elderly population [5, 19-22]. One particularly common device for measuring postural stability is the Neurocom© Balance Master™ system (BM). The BM system uses a force plate platform that localizes an individual’s Center of Gravity (COG) and provides balance and posturography assessments [3, 15, 23-25]. When an individual sways, the vestibulospinal system will perform corrective postural adjustments via the relevant musculoskeletal responses [16]. On such a platform, forces put on the tibialis anterior and triceps surae muscles are key components in the calculation of the Center of Mass (COM) [26]. The BM system been used to interrogate the vestibular system within the elderly population [3, 22, 27-34], stroke patients [35-37], patients with vertigo [38], caffeine consumption [39], Parkinsonian patients [18, 40], patients that experience dizziness [28, 41], spinal cord injury patients [15], cerebellar-pontine-angle-tumor patients [34, 42], concussion patients [43, 44], advanced dementia [3], and patients with traumatic brain injury [23, 43, 45].
The vestibular system consists of the otolith organs of the inner ear and the associated nerves that lead to nuclei within the spinal cord. Specifically, linear accelerations are sensed by the utricle and the saccule, which sense translational motion and gravitational accelerations respectively [46-58]. Studies have shown the otolith organs to primarily be involved with the perception of spatial orientation, determination of the subjective vertical and horizontal, modulation of velocity storage, the vestibulo-ocular reflex during linear movements, and maintenance of postural tonus [52, 54, 57, 59, 60]. These linear accelerometer neurons can also function as a one-dimensional angular velocity detector that would be responsible for the generation of ocular reflexes during linear vertical acceleration [54, 61, 62]. Otolith function may not be as clear-cut, however, due to some otolith-sensitive vestibular nuclei responding to stimulus vectors on a plane (i.e. two dimensions) rather than solely on a horizontal or vertical vector (i.e. one dimension) [54, 61, 62]. This will prove to be important when discussing where Risperidone may have its effect on the vestibular system.

In contrast, the three semicircular canals (horizontal/lateral, posterior, and anterior/superior) provide angular head velocity information [53, 55-58, 63]. The lateral, posterior, and anterior semicircular canals provide information on the rotation of the head around a vertical axis (transverse plane), around an anterior-posterior axis (coronal plane), and a lateral axis (sagittal plane), respectively. Since the otolith organs and semicircular canals occupy a similar anatomical region in the inner ear, and since some stimuli may activate both systems, nerve transmission can overlap. In the common house cat (Felis catus), more than 30% of vestibular neurons receive input from the superior
semicircular canal/otolith nerve pairs while half received input from horizontal semicircular canal/nerve pairs [53, 64, 65]. The superior/otolith pair projected to the ipsilateral lateral and medial vestibulospinal tracts [53, 64, 65]. Although these studies were conducted with cats, one may infer that similar neuroconnectivity occurs in the human with both being in the Mammalian class. The human tracts are more difficult to define and more difficult to trace in postmortem analysis. However, studies comparing other pathways implicated in neurological disease (i.e. vision, somatosensation, and motor tracts) have shown to be relatively conserved in mammals with main differences being the anatomical orientation/organization of specific nuclei and tracts rather than the pathways themselves.

As stated previously, Risperidone has robust D2, 5HT2A, alpha-1, alpha-2, and H1 receptor antagonism along with some excitation of specific vestibular nuclei. More specifically, in terms of vestibular nuclei in relation to specific neurotransmitters, studies have shown: (1) inhibition of the lateral vestibular nucleus (LVN), also known as Deiter’s nucleus, by 5HT derived from the dorsal raphe nucleus [66]; (2) excitation of the inferior vestibular nucleus (IVN) by histamine at H1 receptors [67-69]; (3) an abundance of dopamine and serotonin receptors in the medial vestibular nucleus [70]; and (4) excitation and inhibition of the superior vestibular nucleus (SVN) with 5HT application that is receptor dependent [71]. In terms of vestibular nuclei in relation to specific activation patterns, studies have shown: (1) excitation of the LVN during saccular activation [72]; (2) 15-50% cell activation in the MVN and SVN nuclei during pitch oscillation [73, 74]; and lastly, (3) the activation of 110 cells responding to vertical rotation, 103 in which
were located in the LVN [75] and the rostral portion of the IVN [76, 77]. Effects on the LVN are especially important due to equilibratory reflexes, via the lateral Vestibulospinal tract, associated with it (spinal reflex activity and extensor muscle tone).

Neurocom’s Sensory Organization Test (SOT) of the BM system provides a means by which posturography can be used to test the vestibulospinal pathways that control posture [16, 18, 21, 22, 25, 78]. This is usually accomplished by taking advantage of the two main ways in which people synchronize their movements: (1) the “ankle strategy” which takes advantage of whole body antero-posterior sway through the ankles; and (2) the “hip strategy” which takes advantage of the same sway through the hip [21, 22, 78]. The moving platform (a computer-controlled plate that, in some test conditions, moves in phase with the participant’s pitch rotation) during the SOT tasks challenges maximum anterior-posterior sway angles that effect center of gravity alignment, and the results of the test are presented in the form of an equilibrium score [3, 78]. This is accomplished with: (1) the person’s eyes open or closed; (2) with the platform static or dynamic; and (3) with the surroundings static or dynamic. This creates six potential combinations of dynamical situations. The score is calculated from the theoretical range of antero-posterior sway (12.5 degrees before losing balance) derived from measuring the forces under the feet. This is expressed as a unitless score between 0 and 100 with 100 corresponding to no sway, and a fall corresponding to a score of zero. A score of 100 indicates ankle strategy with no horizontal shear force on the force plate. A score approaching 0 indicates hip strategy with significant horizontal shear forces.
Studies have shown that in the pitch direction, somatosensory input is vital for posture (especially for standing and walking) [16, 35, 79].

Post-hoc, the importance of the superior semicircular canal in relation to the human vestibular system was looked into, and the BM was used to target the superior semicircular canals by applying the SOT. The specific SOT endpoints used were for the subjects’ eyes open as a static control and closed while standing on a platform angulating in the pitch axis, dynamic condition, due to the superior canal responding maximally to sagittal plane rotation.

Risperidone was looked into posthoc to examine effects, if any, on the specific vestibular nuclei associated with the superior semicircular canal. It’s important to note, in a similar study using a 3D turntable, that otoliths were also activated by the perception of head rotation due to the sense of change in direction of the gravity vector [80]. Another study looking into cutaneomuscular reflexes in the anterior and posterior leg, following stimulation of the sural nerve, during tilts in the pitch axis showed crossed reflexes originating from activation of otolith receptors [81, 82]. To this end, studies have shown that there are canal-otolith interactions [83]. More specifically, gravitational vestibular signals from the saccule, as well as pitch rotation from the superior semicircular canal, are interpreted by the vestibular system to create an accurate estimation of tilt and linear acceleration [83]. Due to the outcome of these studies, saccular otolith activation will also be taken into account with respect to Risperidone’s effects on the vestibular system.
It’s important to note that the data collected are used in an attempt to localize vestibular response amongst other systems such as visual, auditory, and somatosensory input. However, one can’t rule out the effects of tactile stimulation (via the plantar surface of the foot) on the moving platform. Such consideration will be taken up during the discussion. The control for vision is vital to the focus on vestibular stimulation. The six external eye muscles are on three perpendicular planes that approximately fit the planes of the three semicircular canals [84]. The vestibulo-oculomotor reflex also has three pairs of subsystems that have an excitatory and inhibitory component. More specifically, the excitatory components pair a specific semicircular canal to specific external eye muscles that create a compensatory eye movement in the plane of the corresponding semicircular canal while the inhibitory component corresponds to the antagonists [85-89]. As a result, compensatory eye movement moves in the opposite direction of angular and/or linear acceleration of the head [90]. Thus, minimizing visual input should decrease the chances of the vestibulo-oculomotor reflex being activated and activating additional circuitry.

With this, this study will build on the understanding of reliable, consistent, and accurate methodologies that are required to assess balance, gait, and the vestibulospinal system. It is hypothesized that the administration of Risperidone will negatively affect equilibrium scores during BM assessment. This is hypothesized due to the drug’s effects on D2 and alpha 2 receptors which are both implicated in balance and posture. Furthermore, assessing gait and balance using mobile sensing devices, with and without
Risperidone, will be used to further future research (i.e. with the decline in semicircular canal and otolith function with age associated with increased postural sway) [91, 92].

**METHODOLOGY**

**Subjects:**

This study was approved by the Institutional Review Board (IRB) and Ethics Committee (EC), and the permit number of IRB is H-34387. All participants provided written consent on their own accord along with written consent in order to participate in the study. The consent process was approved by the IRB. Subjects consisted of 6 males and 6 females (mean age: 25.5 +/- 3.94; range 18-34). Phone interviews were used to assess perspective subject inclusion and exclusion criteria and took approximately 10 minutes to complete. Exclusion criteria included: (1) evidence or history of clinically significant diseases (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing); (2) any condition possibly affecting drug absorption; (3) history of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for men within 6 months of screening; (4) use of tobacco- or nicotine-containing products in excess of the equivalent of 5 cigarettes per day; (5) history of substance abuse and/or dependence; (6) History of movement disorder or family history of movement disorder; (7) history of prior treatment with an antipsychotic agent; (8) treatment with an investigational drug within 30 days preceding the first dose of trial medication; and (8) pregnant women.
For each subjects’ screening, performed at intake, a 12-lead ECG demonstrating QTc <450 msec was needed in order to initiate the study process along with evidence of a signed informed consent document, a Body Mass Index (BMI) of approximately 18 to 30 kg/m² was needed, and vital signs were performed (each task taking approximately 5-10 minutes). Immediately after the intake process, baseline assessment of each subjects’ motor behavior was assessed using the BioSensics, Balance Master, the Tinetti instrument, and the Extrapyramidal Symptom Rating Scale Abbreviated (ESRS-A) (approximately 30-45 minutes to complete).

**Treatment Description and Condition of Evaluation:**

During each subject’s first study date, a dose of 2mg (oral tablet) of Risperidone will be administered immediately after the baseline assessment with post dose assessments occurring at 2 hours post-dose (peak dose), 6 hours post-dose, and 24 hours post-dose using the BalanSens™ system (BioSensics LLC, Cambridge MA), SMART Balance Master™ (NeuroCom, Pleasanton CA), and ESRS-A instruments. An onsite neurologist monitored subjects after the dose was administered. Subjects remained in the laboratory for 7 hours post administration and were released to an accompanying escort. Subjects returned the next day for a follow up, and they performed the same tasks as baseline (30-45 minutes to complete). Participants were given $10 USD for lunch, had access to on site non-caffeinated beverages between tasks, and were allowed to nap, if desired, between assessments.
Protocols were executed and rated by qualified researchers and an onsite clinician. Researchers underwent training on the assessments before being permitted to carry out the protocol.

**Clinical Assessment and Balance Master Assessments:**

The SMART Balance Master system and BioSensics system were used for a series of assessments that included: (1) the Sensory Organization Test (SOT) which gives information on postural control under a variety of sensory conditions; (2) the Adaptation Test (ADT) and Motor Control Test (MCT) which give information on the ability of the automatic motor system to adapt and recover from a loss of balance following unexpected external disturbances; (3) the Limits of Stability (LoS) which is a postural stability test that gives information on the maximum distance a subject can displace their Center of Gravity (COG) without stepping, reaching for assistance, or falling; (4) the ESRS-A; (5) the Tinetti Balance Assessment Tool; and (6) a BioSensics gait task that includes the timed up and go task (TUG).

In this discussion, the SOT is the only endpoint looked into for the BM system, and the other tasks are mentioned here for completion. The SOT, ADT, and MCT tasks assess neurological disease, visual disorders, vestibular disorders, somatosensory disorders, and head injury. The LoS and gait tasks are used to assess musculoskeletal and/or neurological disorders. BioSensics mobile sensing devices were attached to subjects while performed the BM tasks and the ESRS-A.
The ESRS-A was developed to assess a few drug-induced movement disorders including Parkinsonism, akathisia, dystonia, and tardive dyskinesia [93, 94]. The assessment includes analysis for: (1) hypokinetic Parkinsonism; (2) orofacial dyskinesia; (3) trunk/limb dyskinesia; (4) akathisia; (5) tremor; and (6) tardive dystonia [93, 94]. This rating scale rates symptoms from 0-6 in terms of severity and frequency (with higher scores indicating higher severity and vice versa) [93, 94]. The Tinetti was developed to assess fall risk via gait and balance [95, 96]. The assessment includes balance activities such as seated, rising, immediate standing, standing, nudged, eyes closed, turning 360 degrees, and seated [95, 96]. It also includes gait activities such as indication of gait, step length and height, foot clearance, step symmetry, step continuity, path, trunk, and walking time. Each is measured on a scale from 0 to 2 (abnormal to normal), and the total score indicates risk of fall with a score less than or equal to 18 being a high risk, 19-23 a moderate risk, and greater than or equal to 24 a low risk [95, 96].

**Sensory Organization Test:**

The SOT tests one’s ability to use the somatosensory, visual, and vestibular system for postural control. Specifically, sensory organization is the ability to process individual sensory system inputs in order to maintain balance control. This is accomplished by suppressing specific sensory cues, such as vision, and selecting cues that provide maximum information in order to maintain balance. The SOT systematically isolates and quantifies the use of each sensory modality and shows the individuals’ response to each. Information delivered to the subjects’ eyes, feet, and joints are eliminated through calibrated “sway referencing” of the support surface and/or visual
surround which tilt to directly follow the subjects’ pitch sway. By controlling for vision and proprioception through sway referencing and/or eyes open/closed conditions, the protocol eliminates useful visual and/or support surface information [3, 28].

The system computes the Center of Pressure (COP) data which is, as defined by Corbeil, et al. (2012) as “the point of application of the force vector and is equivalent to the sum of all the forces acting between the feet and the platform base.” Such changes in CP show the sway of the subject, along with the subject’s corrective musculoskeletal mechanism, used to maintain his/her Center of Gravity (COG). Subjects were instructed to stand as still as possible with their feet 10 centimeters apart (hip length apart). The six conditions include: (1) eyes open with fixed surrounding and support (somatosensation); (2) eyes closed with fixed support (somatosensation); (3) sway-referenced surroundings with fixed support (somatosensation); (4) eyes open with fixed surroundings and sway-referenced support (vision); (5) eyes closed with sway-referenced support (vestibular); and (6) sway-referenced surroundings and support (vestibular) (Figure 1).
In order to study vestibular inputs exclusively, vision was used as a control and the body was moved with the feet in a fixed position. More specifically, condition 2 and condition 5 were compared to assess the subjects’ ability to use vestibular input to in order to maintain balance [25]. By computing sensory ratios between the average equilibrium scores on this pair of sensory test conditions, vestibular function can be analyzed [25].

Risks:

Electrocardiogram, blood pressure, and vital are taken before the initiation of the study, and subjects are excluded from the study if exclusion criteria are met.
Furthermore, an on-call physician was on-site in the case of a subject(s) having adverse effects to Risperidone. Risks associated with Risperidone include anxiety, somnolence, extra-pyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash and tachycardia in schizophrenia and somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain and urinary incontinence in bipolar mania. There is fall risk associated with BM system and gait tasks; however, to minimize the risk of fall during the BM tasks, subjects are harnessed within the BM system. During gait tasks, a clinician and 2 research assistants were present to monitor and protect the subject from harm.

RESULTS

Statistical analyses were performed using SPSS 20.0.0.1 (IBM, Armonk, NY, USA). Data was not imputed, as subjects were replaced and excluded from analysis if they did not complete the study in full. Equilibrium scores were higher during Condition 2 (Eyes closed, static plate) than during Condition 5 (Eyes closed, dynamic plate), as expected (Figure 2).

A Paired t-test suggests a significant average difference between Condition 2 & Condition 5 Equilibrium scores ($t = 14.1$, $p < .001$). On average, Condition 2 scores were 24.46 points higher than Condition 5 scores (95% CI [20.973, 27.957]) (Table 2).

A Pearson correlation between Condition 2 Equilibrium Score and Condition 5 Equilibrium Score indicated a significant, moderately positive correlation between scores at each timepoint, when paired by subject ($r = .487$, $p < .001$) (Table 3).
A Multivariate Analysis of Variance (MANOVA) indicates a significant effect of Time (p < .001), in addition to a significant interaction between Time and Condition (p < .001) (Table 4). A Trend Analysis suggests that the time trend is Linear (p < .001), and nearly Quadratic (p = .083), in nature (Table 5).

Figure 2: Mean Equilibrium Scores for Conditions 2 & 5 across time
**Paired Samples Test**

<table>
<thead>
<tr>
<th>Paired Differences</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Std. Error</td>
<td>Mean</td>
</tr>
<tr>
<td>Condition 2 – Condition 5</td>
<td>24.46</td>
<td>12.025</td>
<td>1.7357</td>
</tr>
</tbody>
</table>

**Table 1:** Paired t-test between Condition 2 and Condition 5 scores, paired by subject.

**Paired Samples Correlations**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Correlation</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition 2 &amp; Condition 5</td>
<td>48</td>
<td>.487</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Table 2:** Pearson correlation between Condition 2 and Condition 5 across all timepoints
<table>
<thead>
<tr>
<th>Effect</th>
<th>Value</th>
<th>F</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Pillai's Trace</td>
<td>.760</td>
<td>21.103&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Wilks' Lambda</td>
<td>.240</td>
<td>21.103&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Hotelling's Trace</td>
<td>3.165</td>
<td>21.103&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Roy's Largest Root</td>
<td>3.165</td>
<td>21.103&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td>Time * Condition</td>
<td>Pillai's Trace</td>
<td>.673</td>
<td>13.715&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Wilks' Lambda</td>
<td>.327</td>
<td>13.715&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Hotelling's Trace</td>
<td>2.057</td>
<td>13.715&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
<tr>
<td></td>
<td>Roy's Largest Root</td>
<td>2.057</td>
<td>13.715&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.000</td>
<td>20.000</td>
</tr>
</tbody>
</table>

a. Design: Intercept + Condition  
Within Subjects Design: Time  
b. Exact statistic

**Table 3:** Multivariate Tests of Time and Condition
### Tests of Within-Subjects Contrasts

**Measure:** MEASURE_1

<table>
<thead>
<tr>
<th>Source</th>
<th>Time</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Linear</td>
<td>630.972</td>
<td>1</td>
<td>630.972</td>
<td>26.017</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Quadratic</td>
<td>120.751</td>
<td>1</td>
<td>120.751</td>
<td>3.293</td>
<td>.083</td>
</tr>
<tr>
<td></td>
<td>Cubic</td>
<td>115.706</td>
<td>1</td>
<td>115.706</td>
<td>2.325</td>
<td>.142</td>
</tr>
<tr>
<td>Time * Condition</td>
<td>Linear</td>
<td>551.122</td>
<td>1</td>
<td>551.122</td>
<td>22.725</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Quadratic</td>
<td>12.279</td>
<td>1</td>
<td>12.279</td>
<td>.335</td>
<td>.569</td>
</tr>
<tr>
<td></td>
<td>Cubic</td>
<td>104.222</td>
<td>1</td>
<td>104.222</td>
<td>2.094</td>
<td>.162</td>
</tr>
<tr>
<td>Error(Time)</td>
<td>Linear</td>
<td>533.544</td>
<td>22</td>
<td>24.252</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quadratic</td>
<td>806.720</td>
<td>22</td>
<td>36.669</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cubic</td>
<td>1094.822</td>
<td>22</td>
<td>49.765</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4:** Trend Analysis of Within-Subjects Contrasts

### Discussion:

**Interpretation of Abnormal Equilibrium Scores:**

Abnormal equilibrium scores may be due to a variety of confounding variables. Such variables include possible sensory dysfunction that may originate as distal as primary sensory receptor dysfunction or as proximal as a disorder within the central nervous system. However, this is unlikely given the population of healthy volunteer
along with taking into account the inclusion and exclusion criteria. However, a vestibular dysfunction may be present in which in the absence of visual input and/or somatosensory input, the subject has significantly reduced balance. More specifically, this can be tested when comparing SOT condition 5 with the control (condition 2) where the subject is not able to use vestibular cues to maximize balance control.

It’s important to note that unusual body movements that cause abnormal sway can lead to low equilibrium scores. Administrators of the tasks were trained to document any unusual movements that may have had an effect on the equilibrium scores.

**Sensory Effects:**

When a subject is on a stable force plate (SOT condition 2), the following represent the percentage of sensory information one uses to maintain balance: 70% somatosensory; 20% vestibular; 10% visual [16, 97]. When the force plate becomes unstable and somatosensory accuracy was made less accurate through its movements (SOT condition 5), the relative weights shift to: 60% vestibular; 30% visual; and 10% somatosensory [16, 97]. When vision and proprioception were available to the subject, little sway was noted in the population as a whole. In contrast, when vision was blocked, the subjects’ vestibular system took over and the largest sway movement were noted. Thus, when it comes to postural adjustments, vision doesn’t seem to be the prominent sensory modality in comparison to the somatosensory and vestibular pathways.

With this, it can be stated that when the input from a specific sensory modality is compromised, the nervous system will recalibrate in response to its sensory input in order
to reorganize each input’s relative weights in order to maintain postural stability [16].
This is relevant since relevant muscular responses are a product of the CNS updating
postural adjustments in response to sensory input. As an example given by Chien, 2014,
the somatosensory system can’t tell the difference between movement of the force plate
and movement of the body. However, visual input can be used to provide self-motion
information to one’s body that does not reply on information from the support plate [16].
In particular relevance to this study, manipulating vision has been show to affect postural
control exclusively in the sagittal plane and not in the frontal or coronel planes [16, 79,
98]. Studies have shown a reciprocal inhibitory visual-vestibular interaction and has
been implicated as a multisensory mechanism for self-motion perception [99, 100].

It’s important to note that tactile feedback from the plantar surface of the foot may
have an effect on the equilibrium score. Research has shown that such feedback may be
a contributor to balance and postural stability during the static and dynamic tasks of the
Balance Master assessment [12]. Somatosensory stimulation from the safety harness
may also have played a factor [16, 79].

In summary, the central nervous system has multiple sensory modalities that it
uses to ensure that one’s body can remain upright. When the number of modalities made
available increases, integration of modalities ensures that balance and posture can be
maintained via more accurate postural adjustments. Thus, during certain tasks,
modalities that are not as useful are given less weight and vice versa. Such information is
important when taking into account patients with possible vestibular, somatosensory, or
vision disorders.
Relevant Neuroanatomy:

The axons innervating the different vestibular end-organs are distributed to multiple parts to the vestibular cortex with much overlap [101-107]. Axon fibers innervating the saccule are located most laterally in the ascending and descending branches of the vestibular root fibers, and those innervating the utricle are located more medially. From medial to lateral, the anterior, horizontal, and posterior semicircular canal fibers are found. Furthermore, connections between the superior, medial, and spinal vestibular nuclei are reciprocally connected [108]. A future area of research may look into the nucleus paeptorus hypoglossi which receives input from all of the vestibular nuclei as well as the cerebellum, motor pathways specific to controlling eye and head movements, and visual and proprioceptive pathways [109, 110]. Nucleus paeptorus hypoglossi and the perihypoglossal nuclei, and vice versa, project to virtually all parts of the vestibular nuclei [109, 110]

Effects of Atypical Antipsychotics

Subjects who are administered atypical antipsychotics typically show low incidence of observable extrapyramidal symptoms (EPS) [3]. This may be due to lack of precision on the assessments used to assess such symptoms or due to the subjectivity of particular clinician or researcher. As indicated by the ESRS-A compiled results, our population as a whole experienced a very low incidence of EPS. However, two
participants dropped out of the study due to the drug’s effects on their standing balance and due to feelings of vertigo. Other subjects reported similar symptoms but were able to move on with the study.

**Improvements and Future Studies:**

In terms of limitations and possible confounds, anxiety could have been responsible for lower equilibrium scores due to participants being subjected to novel stimuli (e.g. a foreign laboratory environment or a curious pill ingestion). Additionally, there may have been learning effects due to repetitive administrations of tasks (four administrations of experimental protocol in two days). Labs that specialize in molecular neurobiology should build on and focus on the specific nuclei, that may be effected by Risperidone, as described previously.
REFERENCES


69. Yu L, Zhang XY, Cao SL, Peng SY, Ji DY, Zhu JN, Wang JJ: Na(+) -Ca(2+) Exchanger, Leak K(+) Channel and Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel Comediate the Histamine-Induced Excitation


81. Szturm T, Ireland DJ, Jell RM: **Convergent effects from vestibulospinal tract and primary cutaneous afferent fibers on motoneurons to ankle extensor and flexor muscles in humans.** *Experimental Neurology* 1987, **97**(3):529-541.

82. Szturm T, Ireland DJ, Jell RM: **Convergent effects from vestibulospinal tract and primary cutaneous afferent fibers on motoneurons to proximal lower limb flexor and extensor muscles in humans.** *Experimental Neurology* 1988, **99**(1):178-186.


88. Highstein SM: **Synaptic linkage in the vestibulo-ocular and cerebello-vestibular pathways to the VIth nucleus in the rabbit.** *Experimental Brain Research* 1973, **17**(3):301-314.


