Square Wave Jerks and Anxiety as Distinctive Biomarkers for Anorexia Nervosa

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P U R P O S E. The factors contributing to the cause and maintenance of anorexia nervosa (AN) are poorly understood, though increasing interest surrounds the neurobiological underpinnings of the condition. The examination of saccadic eye movements has proven useful in our understanding of the neurobiology of some other psychiatric illnesses, as they utilize identifiable brain circuits. Square wave jerks (SWJs), which describe an involuntary saccade away and back to fixation, have been observed to occur at abnormally high rates in neurodegenerative disorders and some psychiatric illnesses, but have not been examined in AN. Therefore, the aim of this study was to investigate whether individuals with AN and healthy control (HC) individuals differ in SWJ rate during attempted fixation.

M E T H O D S. Square wave jerk frequency was compared across 23 female participants with AN and 22 HC participants matched for age, sex, and premorbid intelligence.

R E S U L T S. Anorexia nervosa participants were found to make SWJs at a significantly higher rate than HC participants. The rate of SWJs in AN was also found to negatively correlate with anxiety. Square wave jerk rate and anxiety were found to correctly classify groups, with an accuracy of 87% for AN participants and 95.5% for HCs.

C O N C L U S I O N S. Given our current understanding of saccadic eye movements, the findings suggest a potential role of γ-aminobutyric acid (GABA) in the superior colliculus, frontal eye fields, or posterior parietal cortex in the psychopathology of AN.

Keywords: anorexia nervosa, square wave jerks, saccadic intrusions, biomarker, neurobiology

A norexia nervosa (AN) is a psychiatric illness characterized by significantly low body weight, a fear of weight gain, and a disturbance in the experience of one’s own body weight or shape.1 A disturbance of body image is a common pathognomonic psychological factor in AN, and perceptual disturbances in the way body shape and weight are perceived are often reported.2 Anorexia nervosa is associated with significant morbidity and has a mortality rate among the highest of any mental illness,3,4 though the factors involved in the cause and maintenance of the illness remain unclear. A wide range of neurobiological findings have been reported in AN, though these are not consistent and a biomarker for the illness has not been identified (for a review see Ref. 5). Eye movements are a potentially useful tool in aiding our understanding of the neurobiology of AN as they utilize identifiable brain circuits. Of particular interest in psychiatric illnesses has been the examination of saccadic eye movements. As humans we use a “saccade and fixate” strategy when viewing our surroundings, typically making three to four saccades every second of our waking lives.6 There is a substantial literature which has examined saccadic eye movement execution in a range of psychiatric illnesses including mood, anxiety, and psychotic disorders (see Refs. 7 and 8 for reviews).

During attempted fixation, saccadic intrusions occur in small numbers in healthy individuals.9 The most widely studied saccadic intrusions are square wave jerks (SWJs), which are pairs of saccades moving the eyes away and returning them to fixation, typically with an intersaccadic interval (ISI) of approximately 200 ms and an amplitude ranging from 0.5 to 8 to as high as 5.10,11 An increased rate of SWJs has been associated with a range of neurodegenerative movement disorders including Huntington’s Chorea and Parkinson’s Disease, suggesting a role of the superior colliculus and basal ganglia in the production of saccadic intrusions.12,13 Abnormally high rates of SWJs are particularly observed in Parkinsonian syndromes with more widespread atrophy such as “Parkinson’s Disease Plus” and Multiple System Atrophy,14 as well as in disorders with cerebellar dysfunction, such as Friedreich ataxia,15 and in individuals with cerebellar and cerebral cortex lesions.16,17 Thus, the neural mechanisms involved in the production of SWJs, and fixation stability in general, appear rather non-specific, with areas of the cerebral hemispheres, basal ganglia,
cerebellum, and superior colliculus potentially involved. Additionally, SWJs can also occur during smooth pursuit.11,18

Few studies have examined the rate of SWJs during fixation in psychiatric populations. An early study by Levin and colleagues19 reported increased saccadic intrusions during fixation in a group of people with schizophrenia. Although the description of these saccadic intrusions closely resembled SWJs, the authors failed to identify them as such.20 A more recent study by Clementz et al.,21 however, reported no group differences in SWJ rate at central or eccentric fixation between participants with schizophrenia and healthy controls (HCs). In contrast, Sweeney et al.22 reported an increased rate of SWJs at central and eccentric fixation in individuals with depression; and although Tien et al.23 reported a trend for obsessive compulsive disorder (OCD) patients to make more SWJs than healthy individuals, statistical significance was not reached. Furthermore, Sweeney et al.18 found significantly more SWJ during pursuit in OCD patients than in controls. It is of interest that studies often report considerable OCD comorbidity in individuals with AN.24,25

The aim of the current study was to identify whether individuals with AN demonstrate difficulties in fixation stability relative to healthy individuals. Given the lack of research in SWJ rate in psychiatric conditions, we proposed an exploratory comparison of SWJ rate between individuals with AN and control participants. An additional aim of the study was to undertake further exploratory analyses between SWJ rate and clinical variables to identify potential relationships between them.

METHODS

This study was approved by the human research ethics departments at The University of Melbourne, Swinburne University of Technology, The Melbourne Clinic, The Austin Hospital, and St Vincent’s Hospital, all in Melbourne, Australia. Informed written consent was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Participants were 24 right-handed females with AN and 24 HCs matched for age and premorbid intelligence quotient (IQ). Technical eye tracking accuracies resulted in the data of one AN and two HC participants being excluded, allowing analyses to be conducted on 23 AN and 22 HC participants. Healthy controls were recruited through public advertisements, whereas AN participants were recruited through public advertisements, the Body Image and Eating Disorders Treatment and Recovery Service at the Austin and St Vincent’s hospitals, and The Melbourne Clinic, all in Melbourne, Australia.

All participants were English speaking, had no history of significant brain injury or neurological condition, no significant ocular pathology and normal (or corrected to normal) visual acuity. Controls were required to have no history of an eating disorder or other mental illness; they were also required to not be taking any medications apart from hormonal contraceptives (10 HC participants were taking this medication). Anorexia nervosa participants were instructed to continue with their normal medications, which were: selective serotonin reuptake inhibitors (SSRIs; 10), atypical antipsychotics (10), benzodiazepines (5), serotonin-noradrenaline reuptake inhibitors (SNRIs; 5), hormonal contraceptives (3), melatonergic antidepressants (2), noradrenergic and specific serotonergic antidepressant (NaSSA; 1), and cyclopyrrolones (1).

The Mini International Neuropsychiatric Interview, 5.0.0 (MINI)26 was used to screen participants for major Axis I psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). It was also used to confirm diagnoses of AN, with the exception of the amenorrhea criterion, which is no longer included in the current DSM-5. Anorexia nervosa was required to be the primary diagnosis of the AN group. Anorexia nervosa participants with comorbid psychiatric conditions, other than psychotic conditions, were not excluded as this would not have represented a typical AN sample.

Premorbid intellect was estimated using the Wechsler Test of Adult Reading.27 Eating disorder symptomatology was investigated with the Eating Disorders Examination Questionnaire (EDE-Q),28 and negative emotional states with the Depression Anxiety Stress Scale (DASS).29

Fixation Task

The fixation task consisted of asking participants to fixate on a one degree white fixation cross against a black background, presented on a rear-projected screen measuring 22'' x 115 cm in front of the participant. They were instructed to fixate for the entire duration of the task (i.e., 5 minutes). The extended duration was used as the data presented here were part of a magnetoencephalographic study of resting state activity, whose results will be presented elsewhere. Eye tracking was recorded using a remote view eye tracker, the EyeLink1000 (SR Research, Ontario, Canada), monocularly at 500 Hz. Data were bandpass filtered between 1.5 and 60 Hz to eliminate slow baseline drift and high frequency noise. Analysis was performed with a custom-made program under Matlab R2014a (Mathworks, Natick, MA, USA). Threshold criteria for SWJ detection included saccade pairs occurring within 200 ms, with amplitudes ranging between 0.1 and 5° (see Fig. 1 for an example).30 Square wave jerks were analyzed for rate, ISI, and amplitude of the first and second saccade of the SWJ pair.

RESULTS

To minimize the effects of fatigue resulting from maintaining constant fixation on a single point, only the first 60 seconds of the fixation task was analyzed. A summary of the results is presented in the Table.
Following data screening and normality checking, one outlier was removed from the AN group and two from the HC group, and a between groups analysis of variance (ANOVA) was performed comparing rate of SWJs. Participants with AN were found to make a significantly increased number of SWJs relative to controls ($F\left[1,40\right] = 9.979, P = 0.003$; Fig. 2).

Pearson’s correlation analyses were performed between the rate of SWJs and each of the DASS subtypes. One further outlier was removed from the HC group who scored high on the depression and anxiety subscales of the DASS (see Fig. 3 for anxiety score distributions). The DASS measures were not found to correlate with the rate of SWJs in the HC control group. The rate of SWJs did not correlate with the depression or stress scores on the DASS in the AN group. However, a significant negative relationship was found for the AN group between SWJ rate and anxiety score ($r = -0.637, P < 0.001$; Fig. 4).

A discriminant function analysis on the entire sample revealed that 87% of AN participants and 95.5% of HC participants were correctly classified based on SWJ rate and anxiety scores (Wilks’ Lambda = 0.359, $\chi^2(2) = 43.083, P < 0.001$).

**DISCUSSION**

Individuals with AN were found to produce a significantly greater number of SWJs during attempted fixation than healthy individuals. In the only other study to examine SWJ rate in AN, Pallanti and colleagues$^3$ did not report a significant difference relative to HCs during a smooth pursuit task. However, that study used electrooculography with inadequate resolution to detect SWJs with amplitudes as small as were seen in our study.

An increased rate of SWJs has not been shown for other psychiatric disorders such as schizophrenia,$^3^2$ affective disor-

### Table. Summary of Results

<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th>SD</th>
<th>n</th>
<th>HC</th>
<th>SD</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>23.14</td>
<td>7.03</td>
<td>23</td>
<td>22.94</td>
<td>3.23</td>
<td>22</td>
<td>0.901</td>
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<td>8.34</td>
<td>23</td>
<td>106.00</td>
<td>7.37</td>
<td>22</td>
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<tr>
<td>BMI</td>
<td>16.54</td>
<td>1.16</td>
<td>23</td>
<td>22.70</td>
<td>5.63</td>
<td>22</td>
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<td>Illness duration</td>
<td>6.83</td>
<td>7.80</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of illness onset</td>
<td>15.96</td>
<td>3.55</td>
<td>23</td>
<td></td>
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<td>EDE-Q restraint</td>
<td>4.02</td>
<td>1.39</td>
<td>23</td>
<td>0.60</td>
<td>0.66</td>
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<tr>
<td>EDE-Q eating concern</td>
<td>3.84</td>
<td>1.23</td>
<td>23</td>
<td>0.25</td>
<td>0.33</td>
<td>22</td>
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<td>EDE-Q shape concern</td>
<td>5.05</td>
<td>0.90</td>
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<td>1.15</td>
<td>0.89</td>
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<tr>
<td>EDE-Q weight concern</td>
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<td>1.40</td>
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<td>0.62</td>
<td>0.80</td>
<td>22</td>
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<tr>
<td>EDE-Q global score</td>
<td>4.37</td>
<td>1.10</td>
<td>23</td>
<td>0.66</td>
<td>0.56</td>
<td>22</td>
<td>0.001</td>
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<tr>
<td>DASS depression</td>
<td>25.52</td>
<td>12.50</td>
<td>23</td>
<td>1.14</td>
<td>1.35</td>
<td>21</td>
<td>0.001</td>
</tr>
<tr>
<td>DASS anxiety</td>
<td>16.22</td>
<td>9.63</td>
<td>23</td>
<td>1.76</td>
<td>2.14</td>
<td>21</td>
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<tr>
<td>DASS stress</td>
<td>25.22</td>
<td>10.35</td>
<td>23</td>
<td>4.14</td>
<td>3.90</td>
<td>21</td>
<td>0.001</td>
</tr>
<tr>
<td>SWJ rate</td>
<td>11.77</td>
<td>12.19</td>
<td>22</td>
<td>2.95</td>
<td>2.78</td>
<td>20</td>
<td>0.003</td>
</tr>
<tr>
<td>SWJ ISI</td>
<td>0.11</td>
<td>0.05</td>
<td>19</td>
<td>0.12</td>
<td>0.04</td>
<td>16</td>
<td>0.743</td>
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<tr>
<td>SWJ amplitude first saccade</td>
<td>0.53</td>
<td>0.25</td>
<td>19</td>
<td>0.58</td>
<td>0.30</td>
<td>16</td>
<td>0.623</td>
</tr>
<tr>
<td>SWJ amplitude second saccade</td>
<td>0.51</td>
<td>0.27</td>
<td>19</td>
<td>0.53</td>
<td>0.29</td>
<td>16</td>
<td>0.852</td>
</tr>
</tbody>
</table>

Square wave jerk ISI is reported in seconds; SWJ amplitudes are reported in degrees; SWJ ISIs and amplitudes are not reported for 3 AN and 4 control participants who made too few or no SWJs. Premorbid IQ, standardized Wechsler Test of Adult Reading Score; BMI, body mass index; Age, age of illness onset and duration illness are reported in years.

**Figure 2.** SWJ rate for AN and HC participants.

**Figure 3.** Anxiety scores on the DASS for AN and HC participants.
unwanted saccades. The rostral superior colliculus in monkeys has been found to result from the fastigial nucleus of the cerebellum to the superior colliculus, but such lesions are also associated with saccadic hypermetria, which was not seen in our AN group (these results are to be reported elsewhere). SWJs have also been associated with a range of cerebral lesions and cerebellar conditions such as Friedreich’s ataxia.

As an increased rate of SWJs may be attributed to a number of areas of the brain, it is not necessarily clear which area underpins this in our AN participants. Areas such as the frontal eye fields (FEFs) and the posterior parietal cortex contain fixation neurons, and deficits in these areas may lead to increased SWJs. The superior colliculus is specifically involved in the inhibition and disinhibition of saccades, with excitatory inputs from the rostral SC projecting to the omnipause neurons, which inhibit the excitatory burst neurons, giving rise to saccades. This mechanism is also thought to play a role in the production of SWJs. Furthermore, the injection of the γ-aminobutyric acid (GABA) agonist muscimol into the rostral superior colliculus in monkeys has been found to result in difficulty maintaining fixation and in the production of unwanted saccades.

The potential role of GABAergic function is further supported by the finding that SWJs were found to correlate negatively with state anxiety. GABA appears to play a significant role in anxiety, leading to anxiolytic treatments such as benzodiazepines being used to enhance GABA transmission in these individuals. Therefore, the findings may be explained by higher GABA activity in nonanxious relative to highly anxious individuals; if this higher GABA activity occurred in areas containing fixation neurons such as the superior colliculus, FEF, or posterior parietal cortex, it could result in an increased rate of SWJs in nonanxious individuals. As we found no significant correlation between SWJ rate and anxiety in HCs, this GABAergic effect may be specific to AN. Alternatively, insufficient between-subject variability in SWJ rate and state anxiety in HCs may have prevented significant correlations in this group.

The classification of groups based on these results, as can be seen in Figure 4, suggests they distinctly differ on these measures and the rate of SWJs relative to state anxiety levels may be a biomarker of AN. It is striking that the AN and control groups can be so well separated using only these two measures. As treatment for AN prioritizes weight-restoration in the first instance, these results may assist us in determining whether individuals are in recovery from the psychiatric aspects of AN and are not merely weight-restored. However, further research in recovered AN is required to determine whether these patterns persist into recovery or whether those recovered from AN perform more similarly to controls. Furthermore, as structural brain changes are often found to improve following weight restoration and recovery, investigating the rate of SWJs in individuals recovered from AN will also allow us to examine whether the state effects of starvation have an influence on results.

A limitation of this study is that spectroscopy was not performed to ascertain the concentrations of GABA and hence its potential role in these findings. To date, the only published studies examining GABA in AN have measured GABA levels in cerebrospinal fluid, and no differences have been reported. Future research combining the techniques used in this study with spectroscopy would increase the value of this research and assist in explaining the findings. Another limitation is that AN patients were not medication-free. Benzodiazepines and atypical antipsychotics have both been found to reduce saccadic peak velocity and gain as well as increase latency, but neither has been reported to induce SWJs. However, to the best of our knowledge, whether benzodiazepines or atypical antipsychotics induce SWJs has not been specifically investigated. Therefore, these medications, particularly benzodiazepines that enhance GABA transmission, may have influenced the findings. Studies of SWJ rate in other clinical populations receiving these medications could help resolve this question.

The results of this study have important implications for our understanding of AN. It appears to share with OCD an increase in SWJ rate but shows in addition a relationship between the rate of these saccadic intrusions and levels of state anxiety. Furthermore, the findings suggest that AN may be related to a dysfunction in a specific brain area or neurotransmitter system, and may help explain some of the difficulties experienced by these individuals. Specifically, the findings suggest a potential role of GABA in brain areas containing fixation neurons such as the superior colliculus, FEF, or the posterior parietal cortex in the psychopathology of AN. Further research into the role of GABA in AN will assist us in confirming the areas of dysfunction in these individuals, and has the potential to lead to the development of more effective treatments specifically targeting these dysfunctions.

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