Autism Spectrum Disorders in Adults and the Autonomic Nervous System: Heart Rate Variability Markers in the Diagnostic Procedure

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1. Background
The heterogeneous appearance of autism spectrum disorders (ASD) in adults poses a major challenge to current diagnostic procedures. Commonly used diagnostic tools are time-consuming and rely on the interpretation of experienced clinicians, which are scarce. This in turn often leads to a delayed onset of suitable measures and increases the level of suffering for the individual.3

Even though the underlying pathomechanism remains unclear, ASD has consistently been associated with dysregulations of the Autonomic Nervous System (ANS).1 Furthermore, Heart Rate variability (HRV) as a measure of ANS activity is known as a promising biomarker in psychiatry and can easily be assessed by recording an electrocardiogram (ECG). If we consider the lack of flexibility and adaptability as a core symptom of ASD and HRV as an index for flexibility and adaptability to stressors, HRV understandably arises as a promising biomarker for the diagnostics of ASD.

2. Objectives and Hypotheses

Based on suspected alterations of the ANS2,4,5,6,7,8,9, the aim of this study was to identify specific ECG derived HRV parameters to allow for a time-efficient, reliable, and marker-based diagnostic approach.

1. We predicted that, based on the core symptom of reduced adaptability, individuals with ASD would show reduced HRV compared to both patients with other psychiatric diagnoses and patients not meeting the criteria for a psychiatric condition.
2. We expected patients with ASD to show reduced parasympathetic activity in comparison to patients with other diagnoses or patients with no diagnosis.

3. Methods

In a cohort of unselected patients presented at a unit for ASD diagnostics, ECGs were recorded to assess the HRV parameters of 152 patients. Following the extensive clinical assessment consisting of explorative clinical interviews, third-party assessments administered by specialised clinicians, interviews with parents or primary carers, and self-reported questionnaires, patients were assigned to one of three groups: ASD (n = 56), any other psychiatric disorder (OD) (n = 72), and individuals not meeting the criteria for psychiatric disorders (ND) (n = 24). (Table 1)

- For the comparison of the HRV parameters between the three groups one-, two-, and three-way ANOVAs were used. Two- and three-way ANOVAs were used to calculate potential interaction effects of age and sex, which were found to differ significantly between the groups.
- Pearson correlations were performed to analyse the relationship between age, self-reported measures, third-party assessments and HRV parameters.
- Finally, receiver operating characteristic curves (ROC) based on regression analyses were calculated to compare the standard diagnostic assessment with the self-reported Autism Quotient (AQ)10 alone, and biological parameters including HRV in terms of diagnostic sensitivity and specificity.

4. Results

**ANOVA**
- Significant differences between patients with ASD and ND were found: ASD showed increased sympathetic activity as assessed by the SNS compared to ND (p = .044). Patients with ASD also had a significantly higher heart rate than individuals with no diagnosis (p = .012).
- Even though not significant, parameters associated with parasympathetic activity (e.g., PNS, RMSSD) suggest an inverted pattern with ASD showing reduced parasympathetic activity compared to ND. (Fig.1)

**Correlations**
- Interestingly, the AQ scores were positively correlated with the SNS index (p = .021, R² = .035) and negatively correlated with the PNS index (p = .013, R² = .041).
- Moreover, the AQ scores were positively correlated with the mean HR (p = .021, R² = .035) and negatively correlated with RMSSD (p = .044, R² = .027).

**ROC**
- Additionally, the accuracy (AUC) of the biological parameters for discrimination between ASD vs. pooled OD/ND was .726 (95% CI = .632 - .820), compared to .697 (95% CI = .613 – .781) for the self-reported AQ alone, and .856 (95% CI = .795 – .917) for the extensive clinical assessment. (Fig.2)

**Conclusion**
Our results confirm the ANS dysregulation in ASD with increased sympathetic activity and reduced parasympathetic as compared to ND. These findings extend the pre-existing evidence for an altered autonomic activity in ASD to more heterogeneous clinical populations. Namely, we found significant differences in HRV between patients with ASD and ND. And even though we did not find significant differences between the HRV of ASD and OD, the pattern of results might nonetheless indicate differences in sympathetic and parasympathetic activity between ASD and OD, as well as OD and ND. This hypothesis is supported by correlation results, revealing that the AO was positively correlated with the SNS index and negatively with the PNS index. This indicates that autistic behaviour as assessed by the AQ score might be associated with a higher sympathetic and a lower parasympathetic activation as assessed by the HRV.

Furthermore, the ROC analyses revealed an acceptable discriminative power of the self-reported AQ score, which to date was only outperformed by an extensive clinical assessment.

Interestingly, the ROC analysis for biological markers only revealed a slightly better discriminative power than the AQ score alone, and was only slightly worse than the extensive assessment. In addition to time and cost efficiency, these findings highlight the clinical advantages of biological markers in ASD diagnostics.

Table 1: Description of comorbidities found in the ASD group and diagnoses of the OD group

<table>
<thead>
<tr>
<th>Comorbidities (ICD-10)</th>
<th>ASD (n = 56)</th>
<th>Diagnosis (ICD-10)</th>
<th>OD (n = 72)</th>
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<tr>
<td>None</td>
<td>38 (67.9)</td>
<td>F32.1, F32.3, F32.4</td>
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<td>F32.0, F33.0</td>
<td>9 (16.1)</td>
<td>F60.0, F61</td>
<td>16 (22.4)</td>
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<td>12 (18.6)</td>
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<tr>
<td>F45.2</td>
<td>7 (12.7)</td>
<td>F45.2</td>
<td>6 (9.1)</td>
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<tr>
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<td>2 (3.6)</td>
<td>F65.0</td>
<td>7 (10.5)</td>
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<tr>
<td>F61</td>
<td>5 (8.7)</td>
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<td></td>
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<td>F12.0</td>
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<td>1 (1.4)</td>
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**References**

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