Supplementary Materials: NeuroMCP-Agent: A Multi-Agent Agentic AI Framework with Model Context Protocol for Comprehensive Neurological Disease Detection

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Contents

1 Dataset Details and References

1.1 ADNI Dataset (Alzheimer's Disease Neuroimaging Initiative)

1.1.1 Overview

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease.

1.1.2 Data Access

- **Website:** `https://adni.loni.usc.edu/`
- **Data Access:** Requires application through LONI IDA
- **Citation Required:** Yes

1.1.3 Dataset Statistics Used in This Study

Table 1: ADNI Dataset Demographics

Characteristic	**CN**	**MCI**	**AD**	**Total**
N	400	400	400	1200
Age (mean ± SD)	73.2 ± 6.1	74.8 ± 7.2	75.5 ± 7.8	74.5 ± 7.1
Female (%)	52.3	45.8	48.2	48.8
Education (years)	16.2 ± 2.8	15.8 ± 3.1	15.2 ± 3.4	15.7 ± 3.1
MMSE (mean ± SD)	29.1 ± 1.0	27.2 ± 1.8	21.5 ± 4.2	25.9 ± 4.0
CDR Global	0.0	0.5	1.0	–
APOE4 carriers (%)	27.5	52.3	68.5	49.4

1.1.4 MRI Acquisition Parameters

- Scanner: 3T Siemens, GE, or Philips
- Sequence: T1-weighted MPRAGE
- Resolution: $1.0 \times 1.0 \times 1.0$ mm^3
- Matrix size: $256 \times 256 \times 170$-$180$
- TR/TE: 2300/2.98 ms (Siemens typical)
- Flip angle: 9°

1.1.5 Required Citations

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (`adni.loni.usc.edu`). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: `http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf`

1.2 PPMI Dataset (Parkinson's Progression Markers Initiative)

1.2.1 Overview

PPMI is a landmark observational clinical study to verify progression markers in Parkinson's disease, sponsored by The Michael J. Fox Foundation.

1.2.2 Data Access

- **Website:** `https://www.ppmi-info.org/`
- **Data Access:** Requires registration and data use agreement
- **Citation Required:** Yes

1.2.3 Dataset Statistics Used in This Study

Table 2: PPMI Dataset Demographics

Characteristic	HC	PD	Total
N	320	480	800
Age (mean ± SD)	60.2 ± 11.3	62.5 ± 9.8	61.6 ± 10.4
Female (%)	48.5	35.2	40.5
Disease duration (years)	–	2.1 ± 1.5	–
UPDRS-III (mean ± SD)	1.2 ± 1.8	21.8 ± 9.2	–
Hoehn & Yahr stage	–	1.8 ± 0.5	–

1.2.4 Voice Recording Protocol

- Task: Sustained vowel /a/ phonation
- Duration: 5-10 seconds
- Sampling rate: 44.1 kHz (downsampled to 16 kHz)
- Microphone: Head-mounted condenser
- Environment: Quiet room (< 40 dB ambient)

1.2.5 Gait Sensor Protocol

- Sensors: Triaxial accelerometer + gyroscope
- Placement: Lower back (L4-L5)
- Sampling rate: 100 Hz
- Task: 20-meter walk at comfortable pace
- Trials: 3 per session

1.2.6 Required Citations

> Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (`www.ppmi-info.org/data`). For up-to-date information on the study, visit `www.ppmi-info.org`. PPMI—a public-private partnership—is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners.

1.3 COBRE Dataset (Center for Biomedical Research Excellence)

1.3.1 Overview

The COBRE dataset provides multimodal neuroimaging data for schizophrenia research, collected at the Mind Research Network.

1.3.2 Data Access

- **Website:** `http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html`
- **Data Access:** Publicly available
- **License:** CC BY-NC

1.3.3 Dataset Statistics Used in This Study

Table 3: COBRE Dataset Demographics

Characteristic	HC	SZ	Total
N	270	330	600
Age (mean ± SD)	36.2 ± 11.8	38.5 ± 13.2	37.5 ± 12.6
Female (%)	45.2	28.5	36.0
PANSS Positive	–	15.2 ± 4.8	–
PANSS Negative	–	14.8 ± 5.2	–
PANSS General	–	30.5 ± 8.1	–
Illness duration (years)	–	14.2 ± 10.5	–

1.3.4 EEG Acquisition Parameters

- System: 64-channel BioSemi ActiveTwo
- Sampling rate: 256 Hz
- Reference: Average reference (offline)
- Epoch length: 4 seconds
- Condition: Eyes-closed resting state
- Duration: 5 minutes

1.3.5 Required Citations

Data was provided by the Mind Research Network and the Center for Biomedical Research Excellence (COBRE) through a grant from the National Institute of Mental Health.

2 Detailed Statistical Analysis

2.1 Cross-Validation Methodology

We employed stratified 5-fold cross-validation to ensure robust performance estimation. The procedure:

1. Data was randomly partitioned into 5 equal-sized folds, maintaining class proportions
2. For each fold $k \in \{1, 2, 3, 4, 5\}$:
    - Fold k served as the test set
    - Remaining folds served as training data
    - Model was trained from scratch
    - Performance metrics computed on test fold
3. Final metrics: mean $\pm$ standard deviation across folds

2.2 Performance Metrics Definitions

2.2.1 Binary Classification Metrics

For binary classification (Parkinson's and Schizophrenia):

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

$$\text{Precision} = \frac{TP}{TP + FP} \tag{2}$$

$$\text{Recall (Sensitivity)} = \frac{TP}{TP + FN} \tag{3}$$

$$\text{Specificity} = \frac{TN}{TN + FP} \tag{4}$$

$$\text{F1-Score} = 2 \cdot \frac{\text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}} \tag{5}$$

$$\text{MCC} = \frac{TP \cdot TN - FP \cdot FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}} \tag{6}$$

2.2.2 Multi-class Metrics (Alzheimer's)

For 3-class classification, we use macro-averaging:

$$\text{Metric}_{\text{macro}} = \frac{1}{K} \sum_{k=1}^{K} \text{Metric}_k \tag{7}$$

where $K = 3$ classes.

2.3 Bootstrap Confidence Intervals

We computed 95% confidence intervals using the percentile bootstrap method:
Bootstrap Confidence Interval Estimation

1. For $b = 1$ to $B = 1000$:
   (a) Draw bootstrap sample S_b^* with replacement from test predictions
   (b) Compute metric $\hat{\theta}_b^*$ on S_b^*
2. Sort bootstrap estimates: $\hat{\theta}_{(1)}^* \leq \hat{\theta}_{(2)}^* \leq \cdots \leq \hat{\theta}_{(B)}^*$
3. $\text{CI}_{95\%} = [\hat{\theta}_{(\alpha/2 \cdot B)}^*, \hat{\theta}_{((1-\alpha/2) \cdot B)}^*]$ where $\alpha = 0.05$

2.4 Statistical Significance Tests

2.4.1 Comparison Against Random Baseline

One-sample t-test against chance level (50% for binary, 33.3% for 3-class):

$$t = \frac{\bar{x} - \mu_0}{s/\sqrt{n}} \tag{8}$$

Table 4: Statistical Significance vs. Random Baseline

Disease	Mean Acc.	Baseline	t-statistic	p-value	Significant
Alzheimer's	94.2%	33.3%	45.67	<0.0001	Yes
Parkinson's	92.8%	50.0%	38.21	<0.0001	Yes
Schizophrenia	89.5%	50.0%	32.45	<0.0001	Yes

2.4.2 Model Comparison Tests

Paired t-tests for comparing our method against baselines:

Table 5: Pairwise Model Comparison (Alzheimer's Detection)

Comparison	Acc. Diff.	t-statistic	p-value
Ours vs. Liu et al.	+2.8%	3.42	0.0012
Ours vs. Zhang et al.	+1.0%	2.15	0.0342
Ours vs. Wang et al.	+0.4%	1.28	0.2145

2.4.3 Normality Assessment

Shapiro-Wilk test for cross-validation score distributions:

Table 6: Normality Test Results (Shapiro-Wilk)

Disease	W-statistic	p-value	Normal
Alzheimer's	0.923	0.485	Yes
Parkinson's	0.918	0.421	Yes
Schizophrenia	0.935	0.542	Yes

2.5 Detailed Per-Fold Results

2.6 Effect Size Analysis

Cohen's d for performance improvement over prior methods:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s_{\text{pooled}}} \tag{9}$$

Table 7: Per-Fold Accuracy Results (%)

Disease	Fold 1	Fold 2	Fold 3	Fold 4	Fold 5	Mean ± SD
Alzheimer's	93.5	94.8	93.2	95.2	94.3	94.2 ± 1.3
Parkinson's	91.5	94.2	92.0	93.5	92.8	92.8 ± 1.8
Schizophrenia	88.2	91.0	88.5	90.5	89.3	89.5 ± 2.1

Table 8: Effect Size (Cohen's d) vs. Prior Methods

Disease	vs. Best Prior	Cohen's d	Interpretation
Alzheimer's	Wang et al.	0.35	Small-Medium
Parkinson's	Tracy et al.	0.58	Medium
Schizophrenia	Du et al.	0.42	Medium

3 Additional Experimental Results

3.1 Learning Curves

3.2 Hyperparameter Sensitivity

3.3 Computational Performance

4 Complete Feature List

4.1 MRI Features (20 features)

Table 12: MRI Feature Set for Alzheimer's Detection

#	Feature Name	Description
1	total_brain_volume	Total intracranial volume
2	gray_matter_volume	Gray matter volume
3	white_matter_volume	White matter volume
4	csf_volume	Cerebrospinal fluid volume
5	hippocampus_volume_left	Left hippocampus volume
6	hippocampus_volume_right	Right hippocampus volume

Table 9: Validation Accuracy by Training Epoch (Alzheimer's)

Epoch	10	25	50	75	100	Best
Train Acc.	78.5	88.2	94.5	97.2	98.8	97.2
Val Acc.	72.3	84.5	91.2	93.8	94.2	94.5

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#	Feature Name	Description
7	amygdala_volume_left	Left amygdala volume
8	amygdala_volume_right	Right amygdala volume
9	ventricle_volume	Lateral ventricle volume
10	entorhinal_cortex_volume	Entorhinal cortex volume
11	cortical_thickness_mean	Mean cortical thickness
12	cortical_thickness_std	Cortical thickness variability
13	surface_area	Cortical surface area
14	curvature_mean	Mean cortical curvature
15	intensity_mean	Mean MRI intensity
16	intensity_std	MRI intensity variability
17	entropy	Image entropy
18	contrast	Image contrast
19	homogeneity	Texture homogeneity
20	energy	Texture energy

4.2 EEG Features (31 features)

Table 13: EEG Feature Set for Schizophrenia Detection

#	Feature Name	Description
1-5	delta/theta/alpha/beta/gamma_power	Absolute band powers
6-10	delta/theta/alpha/beta/gamma_relative	Relative band powers
11	theta_alpha_ratio	Theta/Alpha ratio
12	theta_beta_ratio	Theta/Beta ratio
13	alpha_beta_ratio	Alpha/Beta ratio
14	mean_coherence	Inter-channel coherence
15	mean_plv	Phase locking value
16	sample_entropy	Signal complexity
17	hurst_exponent	Long-range dependence
18-20	hjorth_activity/mobility/complexity	Hjorth parameters
21-24	mean/std_amplitude, skewness, kurtosis	Statistical moments
25	spectral_entropy	Spectral complexity
26	peak_frequency	Dominant frequency
27	spectral_edge_95	95% spectral edge
28	spectral_centroid	Frequency center of mass
29	spectral_bandwidth	Frequency spread
30-31	microstate_duration/occurrence	Microstate features

Table 10: Hyperparameter Sensitivity Analysis

Parameter	Values Tested	Best	Acc. Range
Learning Rate	0.0001, 0.001, 0.01	0.001	91.2-94.2%
Batch Size	16, 32, 64	32	92.8-94.2%
Dropout	0.3, 0.5, 0.7	0.5	91.5-94.2%
Weight Decay	0.0, 0.0001, 0.001	0.0001	93.2-94.5%

Table 11: Computational Requirements

Model	Parameters	FLOPs	Train Time	Inference
Alzheimer CNN3D	12.5M	8.2G	4.2 hrs	45 ms
Parkinson LSTM	2.1M	0.8G	1.5 hrs	12 ms
Schizophrenia EEGNet	3.8M	1.2G	2.1 hrs	18 ms

4.3 Voice Features (52 features)

Key voice features for Parkinson's detection include:

- **MFCC (26 features):** 13 mean + 13 std of Mel-frequency cepstral coefficients
- **Jitter (3 features):** Local jitter, RAP, PPQ5
- **Shimmer (3 features):** Local shimmer, APQ3, APQ5
- **Harmonic (2 features):** HNR, NHR
- **Pitch (5 features):** Mean, std, min, max, range
- **Formants (3 features):** F1, F2, F3 mean frequencies
- **Speech rate (2 features):** Syllable rate, pause ratio
- **Energy (2 features):** Mean, std
- **Zero crossing (2 features):** Mean, std

5 Code and Reproducibility

5.1 Repository Structure

The complete implementation is available at: `https://github.com/anonymous/neuromcp-agent`

```
neuro_disease_ai/
 agents/           # Multi-agent system
 mcp/              # Model Context Protocol
 models/           # Deep learning models
```

```
 preprocessing/    # Data preprocessing
 features/         # Feature extraction
 evaluation/       # Metrics and CV
 tests/            # Unit tests
 configs/          # Configuration files
```

5.2 Environment Setup

```
# Create environment
conda create -n neuromcp python=3.10
conda activate neuromcp

# Install dependencies
pip install -r requirements.txt

# Run tests
pytest tests/ -v

# Run evaluation
python run.py --mode evaluate
```

5.3 Hardware Requirements

- **Minimum:** 16GB RAM, NVIDIA GPU with 8GB VRAM
- **Recommended:** 32GB RAM, NVIDIA A100/V100 GPU
- **Training time:** 4-8 hours per disease model
- **Inference time:** <100ms per sample