

Supplementary Material. Exploring Brain PET Connectivity Data with Machine Learning: A Case Study on Primary Progressive Aphasia

Appendix A1. Local search strategy used in optimization

This section provides a comprehensive overview of the local search strategy integrated into the hybrid ant optimization algorithm employed in this paper. For further details on the implementation of the algorithm see the description provided in the main manuscript.

Algorithm 1 Local search algorithm.

```
Input  $G$ : graph defining the graph structure.  
Input max_depth: local search depth.  
Input paths: array consisting of  $N$  tuples associated to the  $N$  solutions passed to the local search strategy, where the first element of the tuple corresponds to the path found by the ant and the second term to the score given for this path by the objective function.  
for (path, path_score) in paths do  
    depth = 0  
    while depth < max_depth do  
        improvement = False  
        nodes  $\leftarrow$  getReplaceable(path)           ▷ Get those nodes that when removed do not generate two disconnected subnetworks  
        for node in nodes do  
            new_path  $\leftarrow$  remove(path, node)       ▷ Eliminate node from path creating a new path without disconnected subnetworks  
            valid_nodes  $\leftarrow$  valid(new_path,  $G$ )     ▷ Get the nodes that can be added to the network according to the network structure  
            for new_node in valid_nodes do  
                new_sol_temp  $\leftarrow$  add(new_path, new_node)           ▷ Add node to the new path  
                new_score  $\leftarrow$  evaluate(new_sol_temp)             ▷ Evaluate the new path  
                if new_score > path_score then  
                    path  $\leftarrow$  new_sol_temp           ▷ Replace previous solution with new solution  
                    path_score  $\leftarrow$  new_score  
                    improvement = True  
                end if  
            end for  
        end for  
        if !improvement then  
            break  
        end if  
        depth++  
    end while  
end for
```

The application of the local search strategy takes place during each iteration of the algorithm after the ants have finished their respective paths. The primary aim of this search is to improve, in a greedy manner, the objective function's value for the N paths generated by the N top-performing ants.

In the pseudocode described in Algorithm 1, function **getReplaceable** is in responsible for defining which nodes of the initial subnetwork can be replaced without generating two disconnected subnetworks when removed; **remove** for removing the node creating a new solution; **valid** for determining which nodes can be added to the new solution based on the structure of the input network; function **add** for adding a node to the solution; and finally, **evaluate** for evaluating the new solution according to the objective function.

Appendix A2. Classical Graph Theory analysis

This appendix contains the results of the permutation test performed to analyze the statistical differences between the different classical Graph Theory metrics between each progressive primary aphasia (PPA) subtype and healthy controls (HC). All abbreviations used for the different regions of interest (ROIs) can be found in [1]. Left regions are indicated as (L), and right areas as (R).

Table A1: Alterations in brain connectivity between the group of healthy controls (HC) and the semantic variant of primary progressive aphasia (svPPA).

Metric	ROI	svPPA	HC	Difference (absolute value)	p-value
Node degree	PFCventmed (R)	0.103	0.206	0.103	0.001
	SPG (L)	0.072	0.196	0.124	0.002
	SFGmedial (R)	0.062	0.134	0.072	0.003
	AMYG (R)	0.041	0.103	0.062	0.003
Eigenvector centrality	PFCventmed (R)	0.159	0.221	0.062	0.000
	SPG (L)	0.107	0.195	0.088	0.001
	SFGmedial (R)	0.087	0.127	0.040	0.000
	HIP (R)	0.083	0.128	0.045	0.000
	AMYG (R)	0.060	0.091	0.032	0.000
	SFGorb (R)	0.027	0.091	0.064	0.003
Betweenness centrality	PFCventmed (R)	0.036	0.039	0.003	0.000
	SPG (L)	0.026	0.032	0.006	0.000
	MFG (L)	0.025	0.039	0.014	0.002
	THA (L)	0.023	0.025	0.002	0.001
	SFGmedial (R)	0.013	0.014	0.002	0.004
	AMYG (R)	0.010	0.013	0.003	0.002
	IFGoperc (R)	0.004	0.007	0.003	0.003
	HES (L)	0.003	0.007	0.004	0.004
Closeness centrality	PFCventmed (R)	0.075	0.503	0.427	0.000
	SFGmedial (R)	0.045	0.460	0.415	0.005
Average neighbor degree	HIP (R)	0.232	12.357	12.125	0.004

Table A2: Alterations in brain connectivity between the group of healthy controls (HC) and the logopenic variant of primary progressive aphasia (lvPPA).

Metric	ROI	lvPPA	HC	Difference (absolute value)	p-value
Node degree	PFCventmed (R)	0.093	0.206	0.113	0.000
	PFCventmed (L)	0.072	0.175	0.103	0.000
	CAU (R)	0.062	0.124	0.062	0.000
	ROL (L)	0.041	0.093	0.052	0.000
	SFGorb (L)	0.031	0.113	0.082	0.002
Eigenvector centrality	SPG (L)	0.083	0.195	0.112	0.000
	SOG (R)	0.071	0.182	0.111	0.000
	SPG (R)	0.065	0.162	0.097	0.000
	MOG (R)	0.035	0.132	0.097	0.006
	ACC (R)	0.020	0.115	0.095	0.004
	SOG (L)	0.103	0.195	0.091	0.000
	ACC (L)	0.070	0.156	0.086	0.000
	SFGmedial (R)	0.042	0.127	0.084	0.001
	INS (L)	0.085	0.168	0.083	0.000
	PFCventmed (R)	0.139	0.221	0.082	0.000
	OLF (L)	0.084	0.159	0.075	0.000
	REC (L)	0.042	0.105	0.063	0.000
	PFCventmed (L)	0.100	0.156	0.056	0.000
	CAU (L)	0.046	0.100	0.054	0.002
	TPOmid (R)	0.056	0.107	0.052	0.005
	SFGorb (L)	0.034	0.082	0.047	0.000
	IOG (R)	0.059	0.103	0.044	0.000
	CUN (L)	0.067	0.108	0.041	0.000
	CAU (R)	0.062	0.096	0.034	0.000
Betweenness centrality	PFCventmed (R)	0.033	0.039	0.006	0.000
	PFCventmed (L)	0.024	0.030	0.006	0.000
	THA (L)	0.020	0.025	0.004	0.000
	MCC (R)	0.020	0.036	0.017	0.000
	IFGorb (L)	0.016	0.024	0.008	0.007
	MTG (R)	0.015	0.025	0.010	0.000
	IFGorb (R)	0.015	0.032	0.017	0.000
	VER4.5	0.014	0.017	0.002	0.000
	PHG (R)	0.014	0.018	0.004	0.000
	SFGorb (L)	0.011	0.016	0.005	0.000
	VER10	0.010	0.012	0.002	0.000
	CAU (R)	0.007	0.010	0.003	0.002
	ROL (L)	0.007	0.009	0.002	0.000
	IFGoperc (R)	0.005	0.007	0.002	0.000
Closeness centrality	PFCventmed (R)	0.075	0.503	0.427	0.000
	PFCventmed (L)	0.075	0.487	0.413	0.000
	VER4.5	0.068	0.447	0.379	0.001
	SFGorb (L)	0.024	0.431	0.408	0.002
Average neighbor degree	ACC (L)	1.786	14.143	12.357	0.008

Table A3: Alterations in brain connectivity between the group of healthy controls (HC) and the non-fluent variant of primary progressive aphasia (nfvPPA).

Metric	ROI	nfvPPA	HC	Difference (absolute value)	p-value
Node degree	PFCventmed (R)	0.082	0.206	0.124	0.002
	ROL (L)	0.041	0.093	0.052	0.000
Eigenvector centrality	PFCventmed (R)	0.124	0.221	0.097	0.000
	SPG (L)	0.103	0.195	0.092	0.000
	INS (R)	0.100	0.164	0.065	0.001
	OLF (R)	0.098	0.139	0.041	0.000
	SOG (L)	0.093	0.195	0.102	0.000
	OLF (L)	0.078	0.159	0.081	0.000
	IFGorb (R)	0.078	0.148	0.070	0.000
	MOG (L)	0.073	0.141	0.068	0.001
	PHG (R)	0.069	0.122	0.053	0.001
	TPOmid (R)	0.068	0.107	0.040	0.000
	PCL (L)	0.063	0.110	0.048	0.005
	CAU (R)	0.059	0.096	0.037	0.000
	HIP (L)	0.057	0.121	0.064	0.002
	PCUN (L)	0.054	0.123	0.068	0.000
	TPOsup (R)	0.053	0.103	0.050	0.006
	MCC (R)	0.052	0.103	0.050	0.007
	SFGorb (R)	0.030	0.091	0.062	0.001
Betweenness centrality	PFCventmed (R)	0.033	0.039	0.005	0.000
	MFG (L)	0.027	0.039	0.012	0.000
	MCC (R)	0.026	0.036	0.010	0.000
	THA (L)	0.016	0.025	0.009	0.004
	IFGorb (R)	0.015	0.032	0.017	0.003
	MTG (R)	0.014	0.025	0.011	0.000
	VER4.5	0.011	0.017	0.005	0.005
	PHG (R)	0.011	0.018	0.007	0.009
	MTG (L)	0.010	0.020	0.010	0.004
	MOG (L)	0.009	0.021	0.013	0.010
	VER10	0.007	0.012	0.005	0.002
	ROL (L)	0.007	0.009	0.002	0.000
Closeness centrality	PFCventmed (R)	0.049	0.503	0.453	0.007

References

- [1] Edmund T Rolls, Chu-Chung Huang, Ching-Po Lin, Jianfeng Feng, and Marc Joliot. Automated anatomical labelling atlas 3. *Neuroimage*, 206:116189, 2020.