The Neuroanatomy of Developmental Language Disorder

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Introduction

The Problem

The neural substrates of DLD remain unclear

Developmental Language Disorder (DLD): Childhood language problems that are not explained by factors such as hearing deficits or environmental deprivation

As common as ADHD or dyslexia, more so than autism

Previous research on neuroanatomy of DLD

Studies have found abnormalities in many structures: in frontal, temporal, and parietal cortices, and in the basal ganglia and cerebellum.
Which if any structures are consistently abnormal in DLD?

Studies have used a wide range of techniques: structural MRI, post-mortem examination, fMRI, SPECT, fNIRS

Qualitative reviews have not been able to identify consistent abnormalities because of various limitations, including that different studies often:
-have different numbers of participants
-have different sensitivities
-examine different structures

Quantitative syntheses can address these problems

Moreover, the heterogeneity of their included studies suggests greater generalizability of findings

However, coordinate-based neuroanatomical meta-analytic techniques (e.g., ALE) cannot be used for DLD because few DLD studies report coordinates for the whole brain

Methods

Our Solution

A new type of quantitative synthesis.
We examined both the structural and functional neuroanatomy of DLD

Summary of our new approach: Compute
1) *Subject-weighted proportions* of studies *examining* each structure that found *abnormalities* in it
2) *Permutation-based likelihoods* that each anatomical proportion was not due to chance

The approach (CLE: Co-localization Likelihood Estimation) can include studies using *any technique* that examined any structure

We **systematically identified** appropriate studies, and found
1) *22 published peer-reviewed papers* that examined the *structural neuroanatomy* of DLD (using structural MRI or post-mortem examination), encompassing 577 unique participants (DLD: n = 250; TD [typically developing controls]: n = 327)
2) *11 functional imaging papers* (using fMRI, fNIRS, or SPECT), with 414 unique participants (DLD: n = 176; TD: n = 238).

Additional points about CLE:

-Brain is parcellated into various (sub)structures

-Subject-weighted proportions are computed *after merging* studies examining the same subject group, so these groups are not over-counted

-Permutation-based likelihoods take into account the sensitivity and specificity of the different studies

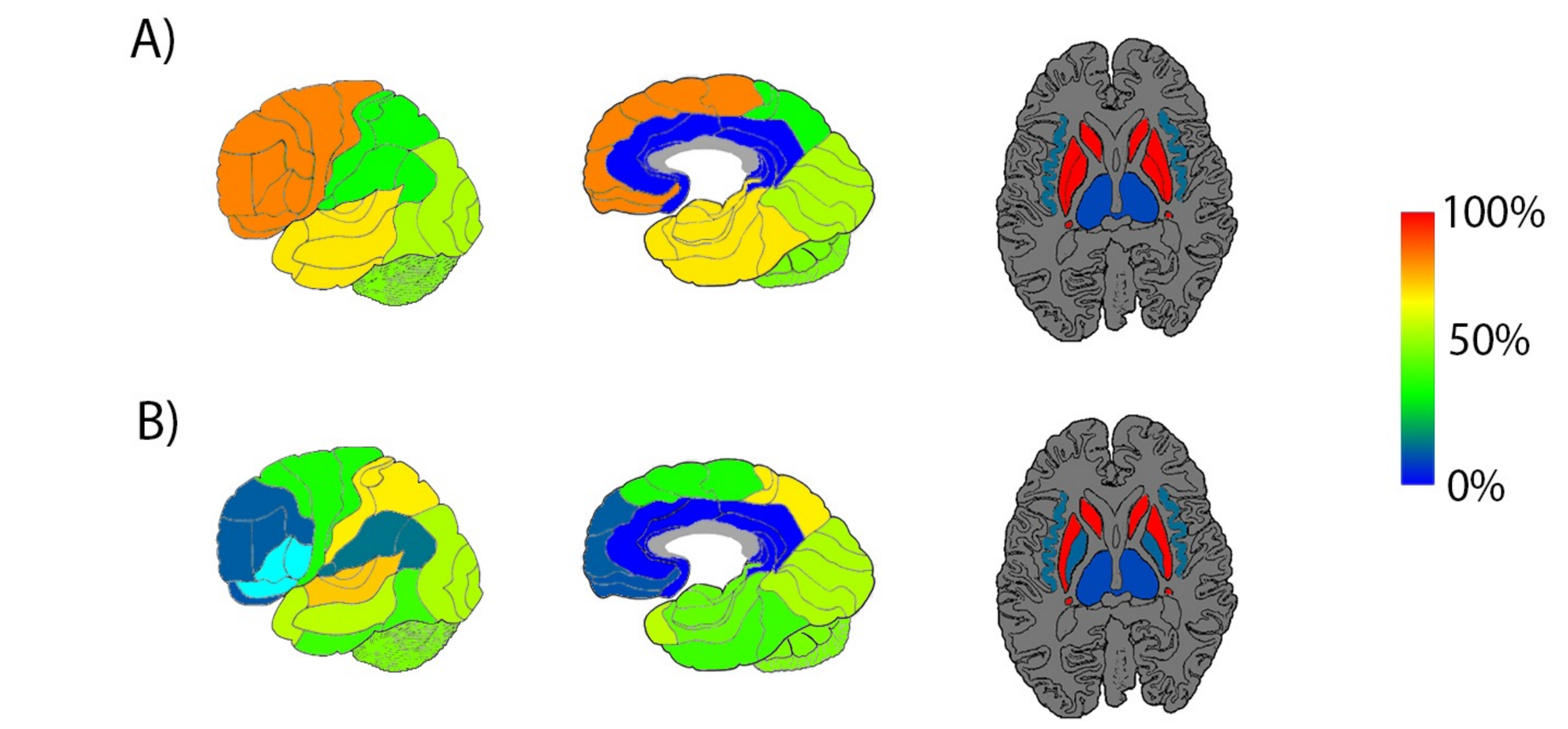
-We computed power for each analysis: Power was almost always high (above 95%, usually above 99%)

Results

Structural neuroanatomical results

Table 1. Structural anomalies in the brain in developmental language disorder

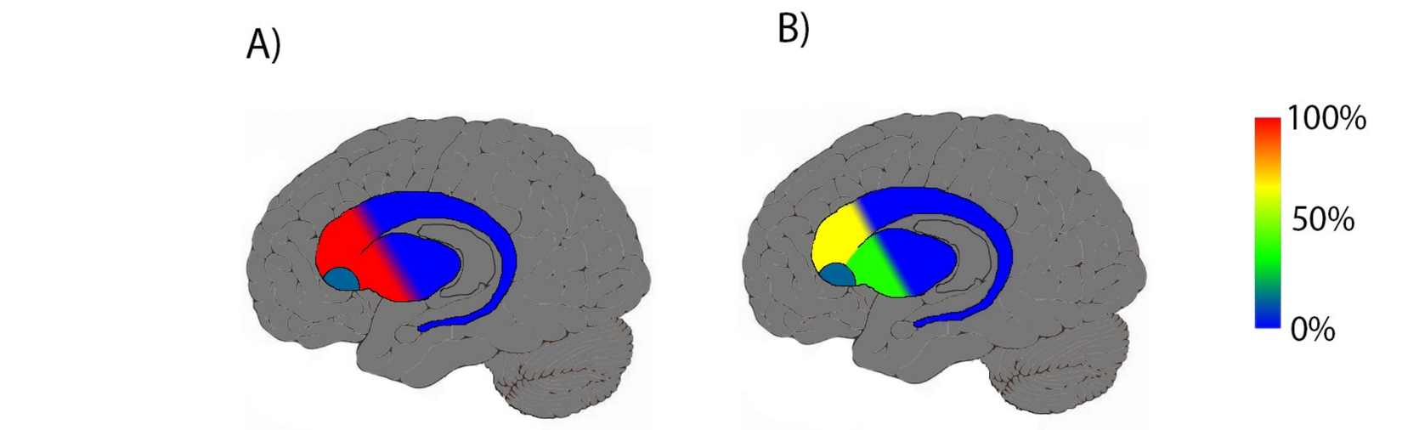
Brain structure	Unique DLD subject groups	# Subjects DLD	# Subjects TD	Weighted proportion of anomalies (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Permutation-based likelihood (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Comparison between left and right
Frontal cortex	13	198	261	82.6	43.4	51.5	97.7	56.4	73.5	63.5
Temporal cortex	12	188	254	69.7	57.0	71.6	90.3	87.9	97.8	69.6
Parietal cortex	15	222	290	34.2	25.4	15.1	18.3	32.6	16.6	65.0
Occipital cortex	8	100	127	56.4	56.6	0	55.0	78.8	0	94.7
Insular cortex	6	80	107	14.4	0.6	16.6	6.9	21.8	26.8	62.1
Cingulate cortex	5	79	107	0	0	0	0	0	0	N/A
Diencephalon/ thalamus	6	100	134	9.0	0	11.7	1.1	0	13.2	62.8
Basal ganglia	7	101	134	100	54.0	68.9	99.8	59.1	84.6	70.5
Cerebellum	5	61	97	48.7	0	54.8	39.8	0	77.7	94.6
Frontal substructures										
Dorsolateral/ polar PFC	7	108	136	12.3	0	0	20.3	0	0	N/A
Orbitofrontal	6	100	128	11.4	13.1	0	11.2	49.4	0	76.2
Motor regions	7	117	128	36.3	41.4	7.9	49.2	74.4	0	93.4
Broca's region	12	197	261	67.0	26.6	51.6	88.1	39.5	87.5	89.1
Temporal substructures										
Superior temporal	11	178	239	73.9	38.5	44.4	96.8	76.2	85.2	58.3
Middle/anterior temporal	8	141	209	58.3	55.6	41.3	70.1	90.0	79.5	69.1
Inferior/ posterior temporal	7	133	201	40.7	0	34.9	33.1	0	59.6	90.1
Medial temporal	7	121	155	45.7	36.4	36.4	71.6	74.2	74.2	N/A
Parietal substructures										
Superior parietal	5	79	107	68.8	62.8	16.7	83.0	91.5	48.9	93.2
Inferior parietal	14	221	290	15.1	3.8	9.8	2.3	0	17.1	63.4
Basal ganglia substructures										
Neostriatum	7	101	134	99.6	54.0	58.7	99.5	79.0	84.8	61.6
Nucleus accumbens	5	76	104	13.3	0	0	4.6	0	0	N/A
Globus pallidus	5	76	104	13.3	0	13.3	4.2	0	29.6	68.9



A) First parcellation level. B) second parcellation level

Table S5. Structural anomalies in neostriatal substructures in developmental language disorder

Brain structure	Unique DLD subject groups	# Subjects DLD	# Subjects TD	Weighted proportion of anomalies (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Permutation-based likelihood (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Comparison between left and right
Caudate nucleus	7	101	134	65.1	54.0	34.5	84.2	81.9	62.0	79.1
Putamen	5	104	76	45.0	7.4	7.4	55.1	0	0	66.6
Anterior neostriatum	4	64	92	100	46.8	53.9	99.8	89.4	92.2	70.0
Posterior neostriatum	4	64	92	0	0	0	0	0	0	N/A
Anterior neostriatum substructures										
Caudate head	4	64	92	63.5	46.8	17.3	93.3	91.8	72.4	83.0
Anterior putamen	4	64	92	36.5	0	36.5	54.5	0	73.1	86.4
Posterior neostriatum substructures										
Caudate body	4	64	92	0	0	0	0	0	0	N/A
Caudate tail	4	64	92	0	0	0	0	0	0	N/A
Posterior putamen	4	64	92	0	0	0	0	0	0	N/A



A) Anterior/posterior neostriatum. B) neostriatal substructures

Main findings: Highly consistent abnormalities found only in the basal ganglia → neostriatum → anterior neostriatum:
- ~100% of subject groups in which these structures were examined, weighted by study sample sizes
- Very high permutation likelihoods (≥ 99.5%) that the anomaly clusterings were not due to chance

Functional neuroanatomical results

Table 2. Functional imaging anomalies in the brain in developmental language disorder

Brain structure	Unique DLD subject groups	# subjects DLD	# subjects TD	Weighted proportion (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Permutation-based likelihood (%) Across Hemispheres	Left Hemisphere	Right Hemisphere	Comparison between left and right
Frontal cortex	13	190	252	63.8	57.4	54.2	73.3	86.1	87.4	48.9
Temporal cortex	11	183	222	35.6	23.5	10.8	21.2	31.4	13.1	58.7
Parietal cortex	11	183	222	80.0	32.1	54.4	98.2	50.8	90.4	83.8
Occipital cortex	6	115	160	56.7	46.5	56.7	57.0	63.1	78.8	67.3
Insular cortex	7	136	178	15.9	0	15.9	0.6	0	32.5	71.1
Cingulate cortex	6	115	160	56.7	14.2	46.5	56.7	27.6	63.6	81.1
Diencephalon/ thalamus	6	115	160	0	0	0	0	0	0	N/A
Basal Ganglia	7	136	178	80.9	24.5	80.9	97.2	45.0	99.9	98.2
Cerebellum	5	111	153	10.6	10.6	0	7.9	22.6	0	68.0
Frontal substructures										
Dorsolateral/ polar PFC	9	147	189	38.1	39.6	44.0	60.6	76.4	78.0	64.4
Orbitofrontal	6	115	160	14.2	14.2	4.0	27.2	52.0	15.4	73.4
Motor regions	7	126	168	59.1	18.9	53.6	85.5	63.7	90.4	87.1
Broca's region	11	183	222	36.3	27.6	18.3	50.4	63.6	49.9	61.2
Temporal substructures										
Superior temporal	11	183	222	35.6	13.5	10.8	48.8	24.7	24.1	47.2
Middle/anterior temporal	6	115	160	4.0	4.0	0	4.8	15.7	0	63.1
Inferior/posterior temporal	6	115	160	10.2	10.2	0	15.2	36.0	0	73.2
Medial temporal	6	115	160	10.2	10.2	10.2	14.9	36.4	36.0	N/A
Parietal substructures										
Superior parietal	8	139	181	16.3	12.7	4.0	22.3	30.3	15.4	56.5
Inferior parietal	10	175	214	73.0	26.3	61.9	98.6	60.8	98.5	92.6
Basal ganglia substructures										
Neostriatum	7	136	178	43.6	12.4	43.6	60.4	31.0	81.4	85.9
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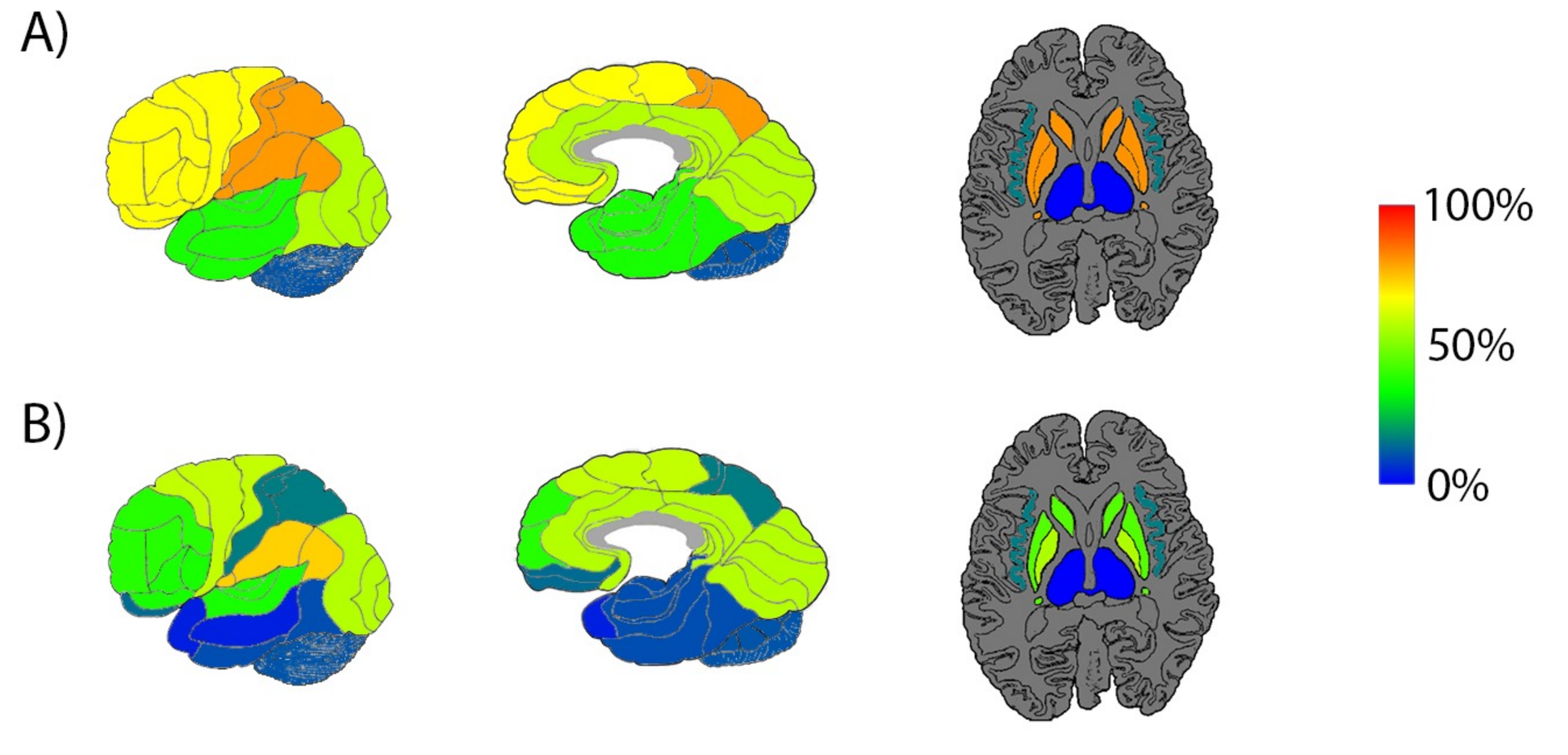

A) First parcellation level. B) second parcellation level

Despite task-dependence of functional activation, functional imaging anomalies occurred mainly in the basal ganglia, as well as in parietal cortex (~80% subject-weighted proportion; > 97% permutation-based likelihood)

Robustness analyses: The structural and functional neuroanatomical results held across robustness analyses: with 1) more lenient and 2) more stringent abnormality inclusion criteria; 3) inclusion of additional (conference/dissertation) studies; 4) in children and adults; 5) before and after 2005 (publication date of Ullman & Pierpont, who proposed basal ganglia abnormalities); 6) with affected members of the KE family included. In all robustness analyses the basal ganglia, neostriatum, and anterior neostriatum showed relatively high proportions of anomalies, where these were examined.

Discussion

Interpretation:

Results suggest **a neuroanatomical account of DLD – like aphasia**

Procedural circuit Deficit Hypothesis (PDH): a neuroanatomical account positing neuroanatomical abnormalities of the neural substrates of procedural memory, in particular the basal ganglia, especially the neostriatum

Indeed, results suggest **abnormalities in the neostriatum, in particular the anterior neostriatum, are a main cause of DLD**: Various genetic and environmental etiologies (e.g., polymorphisms of the *ANKK1, DRD2, CNTNAP2, FOXP2,* and *SEMA6D* genes; thiamine deficiency; prenatal cocaine and nicotine exposure) can yield these abnormalities, which in turn can cause DLD

Other findings:

-anterior neostriatum: caudate head more affected than anterior putamen
-abnormalities not generally left lateralized
-frontal and parietal involvement, but less consistently than basal ganglia
-lack of abnormalities in cerebellum, medial temporal lobe, etc.
-KE family showed same pattern as DLD, plus other abnormalities

Implications:

Suggest multiple lines of DLD research motivated by independent knowledge of basal ganglia, including investigating: dopaminergic involvement; role of direct/indirect basal ganglia pathways; roles of other etiologies affecting neostriatum; status of dorsal stream functions (which may be learned in basal ganglia-based procedural memory); etc.

Translational implications: findings underscore potential of pharmacological (e.g., dopaminergic) and other interventions for DLD that enhance procedural memory and other basal ganglia functions. Diagnostic possibilities.

Language: results elucidate its neural bases, in particular importance of the anterior neostriatum, especially caudate head, including for language learning

Limitations: Other parcellations? Futures studies focus on subcortex too?

Conclusion: **Our new quantitative synthesis approach reveals consistent abnormalities in the basal ganglia, especially the anterior neostriatum, in DLD. The results are reliable, robust, and likely generalizable.**

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