

Network analysis of multiple brain morphometric features in dogs to isolate key driving factors for syringomyelia

ABSTRACT

Syringomyelia (SM) is a painful condition that commonly affects the Cavalier King Charles Spaniel (CKCS) and has **important welfare implications**. Controversy surrounds the development of SM; historically, diagnosis has focused on Magnetic Resonance Imaging (MRI) features of the spinal cord and Chiari-like malformation (CLM), **overlooking potentially relevant features of the brain**. This study set out to test whether any MRI-derived morphometric features of the brain might help explain predisposition of dogs to SM. An **unbiased network analysis approach** was used to evaluate enrichment within 8,432 data points, incorporating clinical data and measurements of brain MRI features in 246 dogs, including 22 CKCSs. **Key findings** included a significant correlation between brain ventricle morphometry and craniofacial shape. A proportion of CKCS dogs clustered independently due to a combination of factors, including **ventricular morphology**. This study has generated a comprehensive analysis of MRI-based brain morphometry in dogs, highlighting **candidate measures to explore further as putative drivers of SM**.

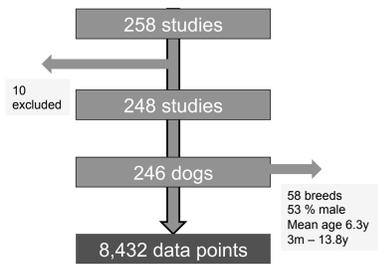
MATERIALS AND METHODS

Approach:

- Network analysis has the power to test previous assumptions about disease mechanisms and the clinical significance of patient-derived observations⁷.
- Network analysis is therefore an ideal tool to evaluate data sets incorporating multiple morphometric measures and other clinical data from dogs.

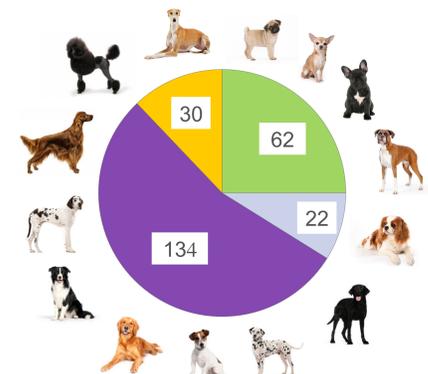
Hypotheses:

- CKCS will cluster independently from other dogs based on brain morphometric features
- Ventricular morphology will drive this clustering

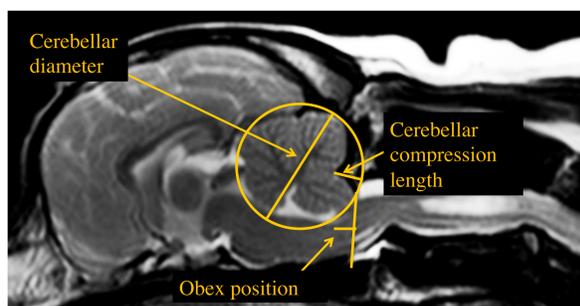


Methods:

- Retrospective analysis of all canine brain MRIs performed over 7 year period at R(D)SVS Hospital for Small Animals
- All dogs underwent MRI for diagnostic purposes, with owner consent
- **Inclusion criteria** - whole brain in transverse and sagittal planes, full clinical history
- **Exclusion criteria** - trauma that would alter skull/brain shape
- **Anonymised** images scored **blind** by two independent observers
- Morphometric brain features measured using OsiriX Medical Imaging software
- Breeds typed by craniofacial shape



- **22 measures** of general brain and ventricular morphology, established measures of CLM, derived measures and normalization factors
- **Matched clinical data** extracted (signalment, body weight, MRI diagnosis)
- **Pre-processing** – numerical values scaled to median for each parameter before incorporation into **MIRU software** (Kajeka)



LIMITATIONS & FUTURE WORK

Limitations:

- Correlative data - causative role of any given factor cannot be confirmed
- Inter-observer variability and few non-CKCS dogs with SM
- Referral selection bias

Future work:

- Incorporate SM scores to determine which brain features correlate most closely with SM
- Overlapped blinded data collection to quantify inter-observer variability
- Validate statistical significance of findings (enrichment analysis)
- Explore parameters that isolate CKCS independently of brachycephaly, and parameters that isolate dogs with SM irrespective of breed.

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CONTEXT

- **CLM-SM** is characterized by malformation (CLM), build-up of fluid within the spinal cord (SM) and a variety of pain-related clinical signs including intolerance to exercise, hypersensitivity to touch, and 'phantom scratching'.
- Observed in up to **95% of CKCS dogs** with estimated heritability of 0.81¹⁻².
- Mechanisms leading to SM remain poorly understood¹⁻².
- **No single published MRI-based measure reliably predicts SM progression**
- Our ability to offer prognostic information and make breeding recommendations to reduce the risk of SM-related pain is therefore limited.
- **Ventriculomegaly** is often present in CKCS and other brachycephalic breeds³⁻⁴ and may correlate better with SM-associated neuropathic pain⁵⁻⁶
- The complexity of CLM-SM however presents a conceptual and statistical challenge
- **Network analysis** is an unbiased, data-driven method that can be used to perform a systematic exploration of patient parameters associated with complex syndromes⁷.



Question:

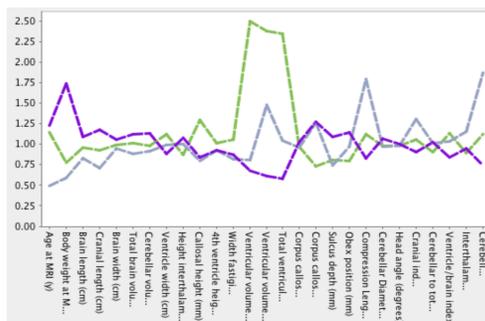
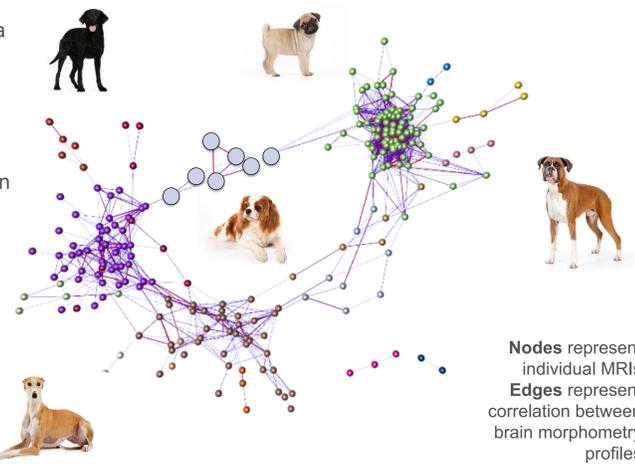
What aspects of *brain* morphology might predispose dogs to syringomyelia?

RESULTS

MIRU takes multidimensional data from each patient, tests the strength of the relationship between each feature for each patient, then clusters patients into groups according to how closely they relate to each other, based on these features.

Preliminary network analysis generated 3 main clusters:

- Cluster 1** (106 dogs; mostly mesocephalic)
- Cluster 2** (77 dogs; mostly brachycephalic including 15 CKCS)
- Cluster 3** (only CKCS)



What drove this clustering?

- Cluster 3 dogs (grey) underwent MRI at a younger age and had a lower craniofacial ratio, brain volume, cerebellar volume and sulcus depth.
- Cluster 3 dogs had higher CLM indices
- Ventricular morphology was the main attribute separating brachycephalic breeds from other breed types
- Ventricular volumes for CKCS dogs were smaller than dogs in cluster 2 (green) and larger than dogs in cluster 1 (purple)

TAKE HOME MESSAGES

- We present a comprehensive analysis of MRI-based brain morphometry in dogs
- Preliminary network analysis clusters brachycephalic breeds on the basis of ventricular morphology
- A proportion of CKCS dogs cluster due to several factors including ventricular morphology
- If these findings are confirmed statistically, our hypotheses would hold true.
- Network analysis has provided a framework for exploring complex - and potentially important - relationships within clinical data that might be missed using conventional statistical modeling
- **This novel approach for handling 'big data' in a clinical context is ideal for multicentre data sharing**, and could have far-reaching impact for evidence-based veterinary medicine, epidemiology, and One Health objectives

References

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