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Water-exchange MRI detects subtle blood-brain barrier breakdown in Alzheimer's disease rats

Ben R. Dickie, Matthias Vandesquille, José Ulloa, Hervé Boutin, Laura M. Parkes, Geoff.J.M. Parker



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**Title:**

Water-exchange MRI detects subtle blood-brain barrier breakdown in Alzheimer's disease rats

**Author names and affiliations:**

Ben R. Dickie<sup>1</sup>, Matthias Vandesquille<sup>1</sup>, José Ulloa<sup>2</sup>, Hervé Boutin<sup>1</sup>, Laura M. Parkes<sup>1,+</sup>, Geoff J. M. Parker<sup>1,2,+</sup>

1. Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine, and Health, Stopford Building, University of Manchester, UK

2. Bioxydyn Ltd, Manchester, UK

<sup>+</sup>Joint senior authors

**Corresponding author:**

[Ben.dickie@manchester.ac.uk](mailto:Ben.dickie@manchester.ac.uk)

**Present address:**

Room G724a  
Stopford Building  
99 Oxford Road  
The University of Manchester  
M13 9PG

**Abstract**

Blood-brain barrier (BBB) breakdown has been hypothesized to play a key role in the onset and progression of Alzheimer's disease (AD). However, the question of whether AD itself contributes to loss of BBB integrity is still uncertain, as many *in-vivo* studies have failed to detect signs of AD-related BBB breakdown. We hypothesize AD-related BBB damage is subtle, and that these negative results arise from a lack of measurement sensitivity. With the aim of developing a more sensitive measure of BBB breakdown, we have designed a novel MRI scanning protocol to quantify the trans-BBB exchange of endogenous water. Using this method, we detect increased BBB water permeability in a rat model of AD that is associated with reduced expression of the tight junction protein occludin. BBB permeability to MRI contrast agent, assessed using dynamic contrast-enhanced (DCE)-MRI, did not differ between transgenic and wild-type animals and was uncorrelated with occludin expression. Our data supports the occurrence of AD-related BBB breakdown, and indicates that such BBB pathology is subtle and may be undetectable using existing 'tracer leakage' methods. Our validated water-exchange MRI method provides a new powerful tool with which to study BBB damage *in-vivo*.

**Keywords:** water-exchange, MRI, blood-brain barrier, Alzheimer's, permeability surface-area product, cerebrovascular dysfunction

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