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Correlation of Inflammation in Arthritis with the Myelination in the Brain

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CORRELATION OF INFLAMMATION IN ARTHRITIS WITH THE MYELINATION IN THE BRAIN

by
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ABSTRACT

This study was conducted to investigate whether the influence of arthritis has an effect on the cerebral white matter. The project was performed at the South Oxford Campus, where diffusion tensor imaging (DTI) data was obtained from the Nathan Kline Institute-Rockland Sample (NKI-RS). Image processing was conducted using Functional Magnetic Resonance Imaging of Brain Software Library in which we obtained raw data to formulate Apparent Diffusion Coefficient (ADC), Axial Diffusivity (AD), Radial Diffusivity (RD), and Fractional Anisotropy. A one way Analysis of Covariance (ANCOVA) was performed to determine the significant difference between the history of arthritis on each of the DTI measures only controlling age (30 years or older) and sex (male and female). There was a significant effect of history of arthritis on ADC, AD, and RD when sex and age was controlled based on the p value significance. It is suggested that the history of arthritis, the effect of inflammation, and possibly medication for arthritis may increase white matter integrity of the cerebrum.

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LIST OF ABBREVIATIONS

ADC	Apparent Diffusivity Coefficient
AD	Axial Diffusivity
ACPA	Anti-Citrullinated Protein Antibodies
CNS	Central Nervous System
RD	Radial Diffusivity
RA	Rheumatoid Arthritis

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disorder. In RA, activated cells and Anti-Citrullinated Protein Antibodies (ACPA) are produced to trigger immune complexes. This causes an overproduction of Tumor Necrosis Factors (TNFs) which is created to fight against infection; however, it "mistakes" infection as its own self (Fisher, Kinloch, Quirke, Venables, et al. 2011).

Causes of RA include genetic factors, periodontal infection, or smoking. Several percentages suggest that genetic factors have a role in the development of RA within an individual. In a family who is at risk, an estimate of 40-50% of seropositive RA was found to be prevalent (Kurko, Besenyei, Laki, Glant, Mikecz, & Szekanecz 2013). In racial groups, it was found that North American Natives display higher rates of RA from about 5-7% (Deane et al. 2017). Following this higher concentration of RA in particular populations, a set of alleles that encode amino acid sequences predicting structural similarities in Human Leukocyte Antigen (HLA) peptide-binding groove help form the shared epitope (SE) which contributes substantially to the pathogenesis of RA and leads to a genetic risk in RA of about 40% (Deane et. al 2017).

A periodontal infection serves as a complement to any system which activates pathogenesis in RA. While the pathogenesis of RA is not well understood, RA is known to need a complement system which includes the periodontal infection (Araujo, Melo, and Lima 2015). The periodontal infection is an inflammatory disease which induces leukocyte infiltration, which causes

destruction to the tissues that support the teeth (Araujo, Melo, and Lima 2015). Based on three prospective cohorts and seven case-control studies, there has been a positive correlation between smoking and RA because smoking can trigger the immune system against ACPAs (Discacciati, Giuseppe, Orsini, and Wolk 2014). While causes may vary or influence one another, it is common that immune complexes are activated in absence of the foreign immunological targets.

In general, RA is found to develop many complications within the human body, mainly affecting the lining of the synovial joints, and it can ultimately lead to disability, premature death, and economic burdens. RA commonly affects the joints in hands, wrists, and knees (Guo, Nossent, Pavlos, Wang, Dan Xu, & Jiake Xu 2018). Symptoms that correlate with the lining of the joint is swelling, redness, deformation of joints, and reduced use of the joint in motion (Guo et al. 2018). Aside from joint damage, RA can also affect other tissues throughout the body such as the heart, lungs, and eyes (Bell 1995).

Increased prevalence of psychiatric disorders in RA has also been shown (Berrigan, Graff, Marriott, Peschken, and Zarychanski et al. 2018). The most common psychological disorders that occur from RA are anxiety disorder, bipolar disorder, and depression. Depression is an important factor to take into consideration when a patient is diagnosed because life after acquiring RA looks different. Individuals with depression loss the ability to carry out daily functions, and the medicine given is strictly for RA and does not help with the onset of depression (Gettings 2010). RA and depression may share pathophysiological mechanisms including the negative effects of proinflammatory cytokines, neurotrophic factors, and measuring of synaptic plasticity (Cavanagh, McInnes, Nerurkar, and Siebert 2018). Cardiovascular Disease (CVD) along with

depression has also been associated with RA. From this, it has been hypothesized that an increase in inflammatory response leads to a vascular resistance which triggers CVD-aggravating behaviors (Bathon, Davidson, Giles, Liu, and Szklo 2015).

It has been shown that psychiatric disorders do not predict an increase in RA, while RA may lead to depression (Nicassio et al. 2010). At the same time, RA has been suggested to reduce the risk of psychosis. It was shown that RA might also be neuroprotective, meaning there is a response in cells to maintain the balance between the ability to give a response required for neuroprotection and repair and the need to avoid autoimmune disease (Cullen, Holmes, Pollak, Blackman, Joyce, Kempton et. al 2019). Also, within a similar study, there was a correlation between having a bipolar disorder and having RA (Hsu CC, Chen SC, Liu CJ, Lu T, Shen CC, et al. 2014). However, in the studies performed relating RA and bipolar disorders, the correlation most likely comes from a connecting factor: smoking (Amital et al. 2016). It is important to note that how these symptoms are induced by RA is unclear, but there are known neurological changes found in RA.

In addition, RA patients show smaller brain volumes compared to controls, whereas it is unclear as to how the brain becomes smaller (Wartolowska et al. 2009). Changes to the brain have been shown to be heterogeneous across types of arthritis. It has been found that knee osteoarthritis (KOA) patients have smaller volumes of bilateral caudate nucleus and hippocampus than those without KOA (Zhi Bai, Cui Mao, Lei Zhang, Qiu Zhang, Xiao Zhang, et al. 2016). The most prominent symptom reported by osteoarthritis patients is chronic pain. Osteoarthritis has a unique brain activation pattern compared to other chronic pain conditions as well as acute pain

(Schnitzer et al. 2010). In RA, the Central Nervous System (CNS) has a prevalent role particularly with cervical myelopathy in atlantoaxial subluxation (AAS). AAS is inflammation in synovial tissue specifically in four synovial articulations between the atlas and axis: two lateral atlantoaxial joints between inferior facet of the lateral mass of the atlas and the superior facet of the axis; and two median synovial joints, one minor between the anterior arch of the atlas and the odontoid process of the axis (Ramos-Remus, Duran-Barragan, & Castillon-Ortiz 2011). CT scans showed spinal cord compression from the loss of posterior subarachnoid space, attenuation of the transverse ligament, and bony and soft tissue change. Aside from RA in the CNS, drugs that treat RA in patients are also related to neurological involvement such as depression, mood disturbances, psychosis, and cognitive dysfunction (Ramos-Remus, Duran-Barragan, & Castillon-Ortiz 2011).

It remains unclear how RA induces the psychological symptoms, whereas it is generally understood that RA results in neurological changes. In this study, we aimed to (1) isolate the white matter regions affected in arthritis, (2) test additional associations between arthritis and the effects it has on different psychiatric disorders, and (3) examine the symptoms and why there is a correlation between brain changes and arthritis.

METHODS

Data Acquisition

First, we acquired DTI data from the Nathan Kline Institute-Rockland Sample which is an open neuroscience model that provides a large neuroimaging database with broad and deep phenotypic measures (NKI-RS:http://fcon_1000.projects.nitrc.org /indi/enhanced/) (Nooner et al., 2012). Participants were recruited with demographics that represent the United States from Rockland County, NY. These participants were asked whether they have or had arthritis as a medical history questionnaire and were also screened for psychiatric, neurological, and chronic medical illnesses. DTI and the presence/absence of arthritis were in the samples from 318 adults 30 years or older (55.89±13.19 range 30 to 85 years old, 85 males and 233 females). 213 individuals did not have a history of arthritis (mean 52.5 yrs old) and 95 individuals were found to have a history of arthritis (mean 63.33 yrs old). Finally, the Institutional Review Board of the University of Mississippi (14x-244) approved the analyses in this study. The DTI series had 128 volumes of non collinear directions as well as 9 volumes without diffusion weighting (TR = 2400ms, TE = 85ms, matrix = 128 × 128, FOV = 256 mm). Each volume consisted of 64 contiguous 2-mm slices with 2mm^3 isotropic resolution.

Data Processing

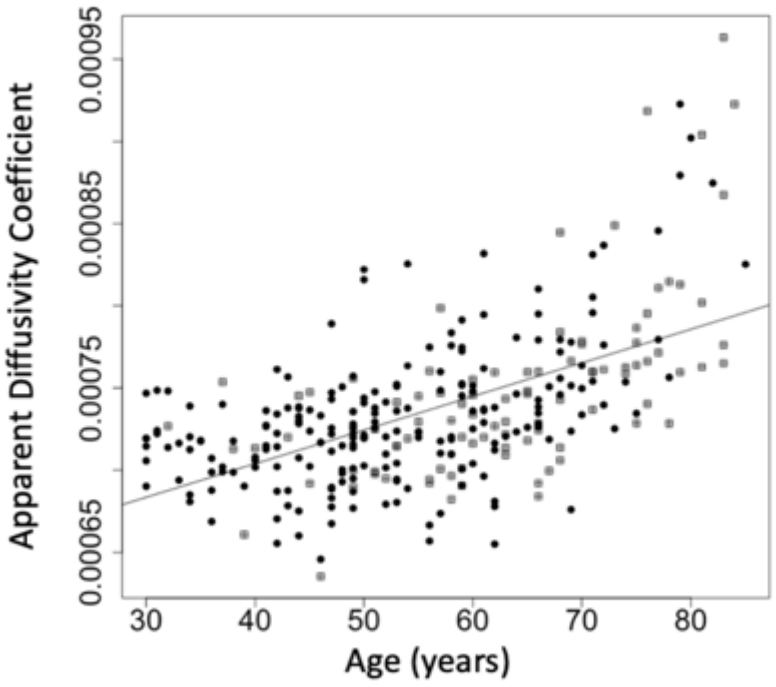
Using the Functional Magnetic Resonance Imaging of the Brain Software Library, the conduction of imaging processing was performed (FSL version 4.1.8; Oxford, United Kingdom; http://fsl.fmrib.ox.ac.uk/fsl). The FSL's Linear Registration Tool was used to correct Eddy-

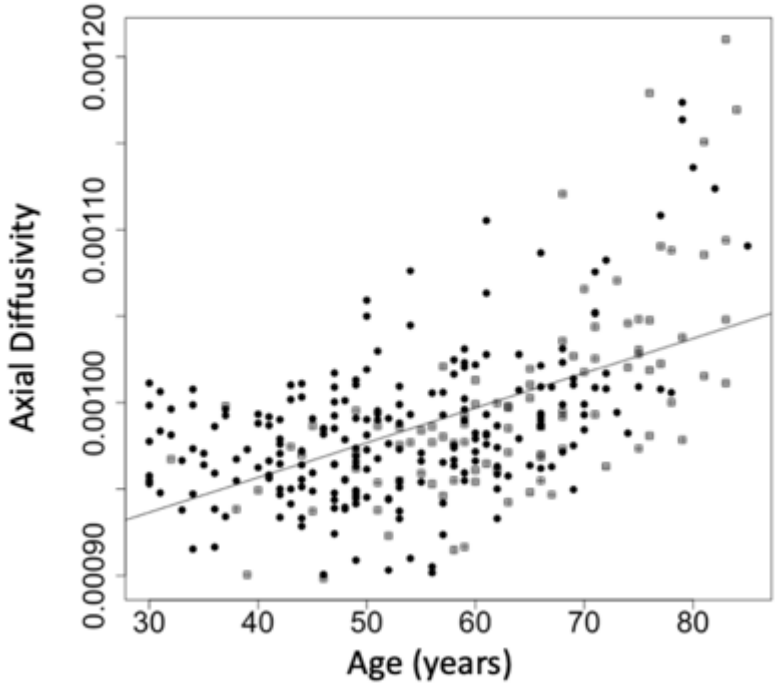
current induced distortions and head-motion displacements through affine registration of the 128 diffusion volumes (b≈1500) to the first b0 volume. Next, The b-vector table (i.e., gradient directions) for each participant was adjusted according to the rotation parameters of this linear correction. FSL's Brain Extraction Tool removed all non-brain tissue. The calculation of ADC, AD, RD, and FA at each voxel of the brain was performed by fitting a diffusion tensor model on to the raw diffusion data while using weighted least squares in FSL's Diffusion Toolbox.

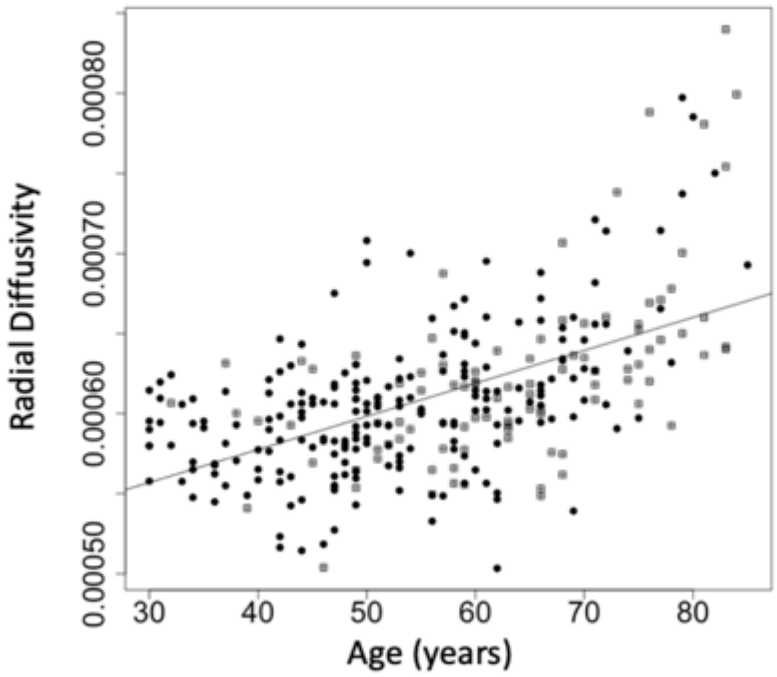
The cerebral white matter was defined by the Harvard-Oxford subcortical atlas (Desikan et al., 2006; Makris et al., 2005) in MNI space (1mm) and linearly registered to the diffusion space in each individual space. The mean ADC, AD, RD, and FA were calculated within the registered white matter. A one-way Analysis of Covariance (ANCOVA) was conducted to determine a statistically significant difference between the history of arthritis on each of the DTI measures (ADC, AD, RD, and FA) controlling for age and sex.

RESULTS

There was a significant effect of the history of arthritis on ADC ($F(1, 304) = 12.29$, $p<0.001$), AD ($F(1, 304) = 9.15$, $p<0.01$), and RD ($F(1, 304) = 12.06$, $p<0.001$) after controlling for age and sex, both of which were significantly associated with ADC, AD and RD. Individuals with a history of arthritis showed lower ADC, AD, and RD. The FA did not show a statistically significant difference.




Axial Diffusivity
0.00090
0.00100
0.00110
0.00120
30
40
50
60
70
80
Age (years)



The positive slope within each graph shows that there is a positive correlation between age and ADC, AD, and RD. This means that as an individual's age increases, the values of ADC, AD, and RD begin to decrease. Also, the p values that were obtained by the analysis were less than .001 signifying there is a change in myelination based on the lower values of ADC, AD, and RD. Before controlling age, the p values were not significant showing us that age has an important factor in arthritis. The ratio for patients with arthritis of women to men is 3:1 which explains why in the study we had 233 females and 85 males who were a part of the study which could have easily increased the prevalence of age to lower ADC, AD, and RD (Kvien, Uhlig, Odegard, and Heiberg 2006).

DISCUSSION

In this study, we sought to examine the influence of arthritis to regions of the brain. Our results showed that AD and RD were lower in individuals with a history of arthritis along with ADC which is the composite measure of AD and RD. Axial diffusivity (AD) is a measure of the movement or diffusion of water molecules along the parallel axis of diffusion, and radial diffusivity (RD) comprises the two vectors of diffusion perpendicular to the diffusion of axial diffusivity. Lower ADC as well as AD and RD suggests that white matter density is being increased by arthritis. The findings here can be interpreted that the myelin sheath facilitates the diffusion of water molecules giving rise to an instrumental part in AD/RD (Ranzenberger 2020).

Based on our results of a substantial decrease within AD, RD, and ADC, these findings are not uniform with other neurological/non-neurological disorders, but it can be understood that there is a change in myelination (Aung, Mar, & Benzinger 2013). Myelination is found to change with the chronicity of the disease. For example, in the early stages of multiple sclerosis, AD decreases while in the later stages AD increases displaying remyelination (Aung, Mar, and Benzinger 2013). Based on our findings, it appears that myelination and/or axons are enhanced.

Our results showed enhanced myelination and/or axons. One possible reason could be that arthritis shows neuroprotective characteristics as shown in a previous study between non-neurological autoimmune disorders and psychosis (Cullen, Holmes, Pollak, Blackman, Joyce,

Kempton et al. 2019). Increased levels of T reg cells in arthritis would likely lead to an increase in neuroprotection which signals specific T cells via immunization with myelin-based proteins or pre-activated myelin basic protein-specific T cells signaling an overall increase in myelination (Walsh, Watson, & Kipnis 2014). The increased levels of myelin could also demonstrate an active remyelination process from a previous injury in which potential previous diseases or injuries were not taken into account (Spader, Dean, LaFrance, Rauker, Cosgrove, Eyerly-Webb et. al 2018).

From here, another conclusion can be made based on observing data from various experiments on the relation between non-neurological autoimmune disorders and psychosis. Significant negative single nucleotide polymorphism-genetic correlation is seen between schizophrenia and seropositive cases of RA which identified single nucleotide polymorphisms with potential pleiotropic effects for both RA and schizophrenia which is where allelic variants of same gene increase the risk for other disorders. This altogether is consistent with the negative correlation between psychosis and RA (Cullen, Holmes, Pollak, Blackman, Joyce, Kempton et al. 2019).

In addition to our results, it is important to note that other studies suggest arthritis medication itself can have an effect on enhancing myelination and causing neurological disorders as well displaying another source behind the effects seen within the CNS. In this particular study, a high dosage of corticosteroid induced psychosis in patients with RA. Corticosteroid is a steroid hormone used to treat inflammation, and a good example is prednisolone (George & Ward 2016). In another study, it was found that patients who frequently take NSAIDs (Nonsteroidal anti-inflammatory drugs, which are often used to alleviate pains in RA) suppress the RhoA

signal which improves axonal growth and myelination after a traumatic injury. After a CNS injury, the intracellular pathway of activation of RhoA restricts axonal growth, which includes myelin. Therefore, the best approach to enhance axonal growth or myelin is to administer NSAIDs, which in turn overcomes neuronal growth suppression from axonal growth inhibitors and represses activity of RhoA (Xing, Li, Wang, Mukhopadhyay, Fisher, Gilpin et. al 2011). As we do not have precise records of medications in our study, we are not able to determine whether medications played a greater role than RA itself.

Limitations

A further experiment would test the specific types of arthritis as well as record the medical history. While I obtained data that separated sex and age, it did not include the types of arthritis which could impact the increase in myelination and the relation of arthritis with psychosis. Therefore, I would recommend when gathering random individuals and separating them based on history of arthritis, I would also further separate them based on medications they are taking as well as the types of arthritis as well as how long they have had arthritis. Seeing how myelination is based on the degree of chronic illness, it would be helpful to differentiate between the degree of inflammation and observe active/inactive lesions on an MRI.

Conclusion

In this study, individuals with a history of arthritis showed greater AD and RD as well as ADC in the cortical white matter. It is suggested that RA or RA medications may enhance myelination and/or axons in the brain.

LIST OF REFERENCES

Acute and chronic changes in myelin following mild traumatic brain injury. (2018, May 1). Retrieved from https://www.sciencedaily.com/releases/2018/05/180501085536.htm

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007, July). Diffusion tensor imaging of the brain. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2041910/

Aung, W. Y., Mar, S., & Benzinger, T. L. (2013). Diffusion tensor MRI as a biomarker in axonal and myelin damage. *Imaging in Medicine*, *5*(5), 427–440. doi: 10.2217/iim.13.49

Axial Diffusivity. (n.d.). Retrieved from https://www.sciencedirect.com/topics/immunology-and-microbiology/axial-diffusivity

Bell, C. L. (1994). Rheumatoid arthritis. *Postgraduate Medicine*, *95*(4), 127–140. doi: 10.1080/00325481.1994.11945823

Braun, H. J., & Gold, G. E. (2012). Diagnosis of osteoarthritis: Imaging. *Bone*, *51*(2), 278–288. doi: 10.1016/j.bone.2011.11.019

Cullen, A. E., Holmes, S., Pollak, T. A., Blackman, G., Joyce, D. W., Kempton, M. J., … Mondelli, V. (2019). Associations Between Non-neurological Autoimmune Disorders and Psychosis: A Meta-analysis. *Biological Psychiatry*, *85*(1), 35–48. doi: 10.1016/j.biopsych.2018.06.016

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., … Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral

cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Fuggle, N. R., Howe, F. A., Allen, R. L., & Sofat, N. (2014). New insights into the impact of neuro-inflammation in rheumatoid arthritis. *Frontiers in Neuroscience*, *8*. doi: 10.3389/fnins.2014.00357

Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N. J., & Xu, J. (2018). Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Research*, *6*(1). doi: 10.1038/s41413-018-0016-9

Hsu, C.-C., Chen, S.-C., Liu, C.-J., Lu, T., Shen, C.-C., Hu, Y.-W., … Hu, L.-Y. (2014). Rheumatoid Arthritis and the Risk of Bipolar Disorder: A Nationwide Population-Based Study. *PLoS ONE*, *9*(9). doi: 10.1371/journal.pone.0107512

Hultqvist, M., Olofsson, P., Holmberg, J., Backstrom, B. T., Tordsson, J., & Holmdahl, R. (2004). Enhanced autoimmunity, arthritis, and encephalomyelitis in mice with a reduced oxidative burst due to a mutation in the Ncf1 gene. *Proceedings of the National Academy of Sciences*, *101*(34), 12646–12651. doi: 10.1073/pnas.0403831101

Jang, S. H. (2018). Traumatic Axonal Injury in Patients with Mild Traumatic Brain Injury. *Traumatic Brain Injury - Pathobiology, Advanced Diagnostics and Acute Management*. doi: 10.5772/intechopen.70988

Kurkó, J., Besenyei, T., Laki, J., Glant, T. T., Mikecz, K., & Szekanecz, Z. (2013). Genetics of Rheumatoid Arthritis — A Comprehensive Review. *Clinical Reviews in Allergy & Immunology*, *45*(2), 170–179. doi: 10.1007/s12016-012-8346-7

Kvien, T. K. (2006). Epidemiological Aspects of Rheumatoid Arthritis: The Sex Ratio. *Annals of the New York Academy of Sciences*, *1069*(1), 212–222. doi: 10.1196/annals.1351.019

Makris, N., Kennedy, D. N., Mcinerney, S., Sorensen, A. G., Wang, R., Caviness, V. S., & Pandya, D. N. (2004). Segmentation of Subcomponents within the Superior Longitudinal Fascicle in Humans: A Quantitative, In Vivo, DT-MRI Study. *Cerebral Cortex*, *15*(6), 854–869. doi: 10.1093/cercor/bhh186

Mao, C. P., Bai, Z. L., Zhang, X. N., Zhang, Q. J., & Zhang, L. (2016). Abnormal Subcortical Brain Morphology in Patients with Knee Osteoarthritis: A Cross-sectional Study. *Frontiers in Aging Neuroscience*, *8*. doi: 10.3389/fnagi.2016.00003

Nicassio, P. M. (2010). Arthritis and psychiatric disorders: Disentangling the relationship. *Journal of Psychosomatic Research*, *68*(2), 183–185. doi: 10.1016/j.jpsychores.2009.09.008

Nishioku, T., Furusho, K., Tomita, A., Ohishi, H., Dohgu, S., Shuto, H., … Kataoka, Y. (2011). Potential role for S100A4 in the disruption of the blood–brain barrier in collagen-induced arthritic mice, an animal model of rheumatoid arthritis. *Neuroscience*, *189*, 286–292. doi: 10.1016/j.neuroscience.2011.05.044

Nooner, K. B., Colcombe, S. J., Tobe, R. H., Mennes, M., Benedict, M. M., Moreno, A. L., … Milham, M. P. (2012). The NKI-Rockland Sample: A Model for Accelerating the Pace of Discovery Science in Psychiatry. *Frontiers in Neuroscience*, *6*. doi: 10.3389/fnins.2012.00152

Quirke, A.-M., Fisher, B. A., Kinloch, A. J., & Venables, P. J. (2011). Citrullination of autoantigens: Upstream of TNFα in the pathogenesis of rheumatoid arthritis. *FEBS Letters*, *585*(23), 3681–3688. doi: 10.1016/j.febslet.2011.06.006

Schnitzer, T., & Apkarian, A. (2010). I-20 Impact Of Osteoarthritis Pain On The Brain. *Osteoarthritis and Cartilage*, *18*. doi: 10.1016/s1063-4584(10)60025-8

Walsh, J. T., Watson, N., & Kipnis, J. (2014). T cells in the central nervous system: messengers of destruction or purveyors of protection? *Immunology*, *141*(3), 340–344. doi: 10.1111/imm.12187

Ward, L., & George, J. (2016). Corticosteroid-induced psychosis in rheumatoid arthritis. *Progress in Neurology and Psychiatry*, *20*(5), 13–15. doi: 10.1002/pnp.441

Wartolowska, K., Hough, M. G., Jenkinson, M., Andersson, J., Wordsworth, B. P., & Tracey, I. (2012). Structural changes of the brain in rheumatoid arthritis. *Arthritis & Rheumatism*, *64*(2), 371–379. doi: 10.1002/art.33326

Xing, B., Li, H., Wang, H., Mukhopadhyay, D., Fisher, D., Gilpin, C. J., & Li, S. (2011). RhoA-inhibiting NSAIDs promote axonal myelination after spinal cord injury. *Experimental Neurology*, *231*(2), 247–260. doi: 10.1016/j.expneurol.2011.06.018

Yau, T., Ranzenberger, L., Capannolo, L., Rodriguez, A., & Snyder, T. (2019). Shoulder MR Arthrography Complication – Direct Injection of the Biceps Tendon: A Case Report. *Journal of Medical Imaging and Case Reports*, *3*(2). doi: 10.17756/micr.2019-030