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Structural Imaging in Cluster Headache

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Abstract Cluster headache is a rare primary headache disorder and the most common trigeminal-autonomic cephalalgia. Even though it has been extensively studied, its pathophysiology remains nebulous. Over the last two decades, cerebral imaging has increasingly been used to aid the investigation of pain and headache disorders. Pioneering work using magnetic resonance-based, voxel-based morphometry depicted an isolated increase of grey matter in the posterior hypothalamus and thereby reconfirmed the most commonly accepted pathophysiological concept. More recent works demonstrate structural changes across multiple structures related to pain processing, sensory integration, and emotional evaluation. These changes do not seem to be static, but rather appear to be dynamic in nature as they change over the course of the disease. This was interpreted as a reflection of the plasticity of the human brain and should guide future thoughts towards a more complex pathophysiological model involving a maladaptive pain modulatory network.

Keywords Cluster headache · Voxel-based morphometry · DTI · TBSS · Neuronal plasticity · Hypothalamus

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Introduction

Trigeminal autonomic cephalalgias (TACs) are characterized by recurrent episodes of excruciatingly painful, unilateral headache attacks typically accompanied by ipsilateral trigeminal autonomic symptoms including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema [1]. In cluster headache (CH) the headache attacks usually last from 15 to 180 minutes and may occur from once every other day up to eight times a day. Even though CH is the most common TAC, the condition is rare, which makes studies on this topic challenging.

Today's pathophysiological concepts of CH are based on assumptions generated by different methods including clinical observation, therapeutic success with different medications, imaging, electrophysiological and endocrinological studies, as well as symptomatic cases of CH. Due to the clinical observation that CH shows a distinct pattern of headache occurrence with circannual and circadian rhythmicity, and based on the response to lithium-therapy, an important role of the hypothalamus in the underlying pathophysiology was discussed from early on. This assumption was supported by neuroendocrine dysfunction observed in 1990 [2]. Electrophysiology revealed CH to be a condition with altered trigeminal nociceptive processing mainly based on central facilitation [3, 4] and functional imaging showed activation of areas involved in pain processing and pain modulation, including the hypothalamus [5–8].

The method that probably most influenced today's pathophysiological model of CH was structural brain imaging using magnetic resonance-based, voxel-based morphometry (VBM). This is without critique, since results from VBM studies are often diverse and sometimes quite controversial mostly due to the lack of understanding the underlying

physiological and anatomical correlates of the method itself—a challenge that many new imaging techniques face.

However, imaging in general is of very frequent use in headache and pain research. Functional imaging is well-validated, and positron-emission-tomography (PET) as well as functional magnetic resonance imaging (fMRI) are widely accepted to indirectly show neuronal/cellular activity within the human brain. Unfortunately, such an acceptance does not account for structural imaging. On one hand, multiple variables may influence the results of studies using these methods and they are not neuroanatomically nor histologically validated. Most important is that the term structural imaging does not necessarily relate to actual changes in neuronal numbers or density in regard to neurogenesis or apoptosis, as is often discussed in structural imaging manuscripts. Instead it may rather entail changes in glial cells, intracellular or extracellular fluid shifts, or other transient mechanisms on a cellular level. This may essentially change the interpretation of structural imaging studies in the future and may lead to reconsideration of knowledge ascertained from the past.

Symptomatic Cluster Headache

Cluster headache is a primary headache disorder and not a symptomatic condition. Since multiple symptomatic cases were described, most guidelines recommend MRI to rule out underlying pathologies. Most authors refer to symptomatic headaches with a cluster-headache phenotype or cluster-like-headache (CLH), but the expression symptomatic CH is used as well. Multiple different pathologies were identified and associated with such CLHs. Since this is not the primary focus of this article and is worth an article on its own, which was recently published [9], we will only briefly summarize some of the cases and findings.

From 1975 to 2008, 156 CLH cases were published. Many of these reports did not provide sufficient information but approximately one-half appear to be perfect mimics of primary CH fulfilling ICHD-2 criteria [10].

In regard to etiology, most of the reported pathologies where of vascular (38 %), tumorous (25.7 %), or inflammatory/infectious (13.5 %) origin, or the headaches were related to a trauma (8.8 %).

In regard to localization of the pathology, many cases with close proximity to the hypothalamus were published during the last decades (e.g., pituitary [11–13], sella [14], third ventricular [15], cavernous [16], anterior communicating artery [13], or sphenoidal [17] pathologies). But there are nearly as many cases with complete fulfilment of ICHD2 criteria with pathologies in different locations (e.g., Herpes zoster ophthalmicus [18], upper cervical meningioma [19], facial herpes simplex [20], frontal skull fracture [21], carotid artery aneurysm [13], fronto-temporal-parietal subdural haematoma [22], epidermoid tumur of the posterior fossa [23], vertebral aneurysm [24], post-tonsillectomy, trigeminal neurinoma [25], dental extraction [26], foreign body in the maxillary sinus [27], and intraocular lens implant [28]).

All these symptomatic cases are of high interest, but they do not seem to share an obvious common pathophysiological pathway that would help us to better understand the mechanisms associated with or leading to the development of cluster headache. In some cases it might just be coincidence, in others the pathology may be just enough to lift a potential "subclinical"-CH over a certain threshold to become clinically apparent or relevant. Interestingly, at least 12 of the reported cases fulfilling ICHD-2 criteria ceased completely after surgery [9].

The cases reported may enrich pathophysiological thoughts as Straube did in 2007, raising the question of imbalance in the autonomic system as contributor to the development of CH [29]. But none of these can clarify primary CH pathophysiology.

Either way, it is interesting that, for example, brainstem/cervical spine lesions as well as ophthalmological, maxillary sinus, dental, or cortical (fronto, temporo, parietal subdural haematoma) pathologies are capable of causing the typical clinical picture of CH.

Voxel-Based Morphometry (VBM)

Voxel-based morphometry (VBM) is the structural imaging method most frequently used for the investigation of CH. Very early pioneering work done by May and colleagues [5] inspired headache and pain researchers all over the world to use VBM for the their research. VBM was used in multiple pain and headache conditions with very diverse and sometimes even controversial results. The main finding and common denominator of most studies conducted so far, regardless of the type of pain, is that ongoing pain appears to be associated with grey-matter (GM) volume decrease distributed over multiple brain areas (see reviews [30, 31]). GM changes described in different conditions over numerous studies were distributed over many different areas that sometimes overlapped but often did not reconfirm previous findings. At least two studies in pain research showed these changes to be reversible [32, 33]. Consequently, the alterations identified should not be regarded as GM damage or loss but seem to be associated with adaptation mechanisms of the adult human brain in response to the experience of pain in general and the underlying pain or headache disorder in particular. Many brain areas affected of this GM decrease were also found in functional imaging experiments in spontaneous as well as experimental pain [5, 6, 34, 35]. This observation indicates that GM structural changes follow the functional reactions of the brain to painful stimuli or conditions, but may extend beyond mere functional short-term changes and possibly represent long-term

adaptation effects to pain. However, it should be acknowledged that pain is not a specific stimulus to cause these areas to activate, as other sensory input may also activate secondary processing centers, so that some of these changes are associated with pain but are not exclusively related or caused by pain at all.

In the first VBM study on CH, the authors investigated 25 patients suffering from episodic and chronic CH (14 of those in an active headache phase) and their brain scans were statistically compared to those of 29 healthy controls (HC) regarding GM density [5]. The authors detected isolated GM increase in the bilateral inferior-posterior hypothalamus ($p<0.001$). Even for the smaller subgroups (active headache phase and outside bout vs. healthy controls) this alteration was still observable. In a mirrored analysis in which images were flipped to the affected headache side, GM change was found to be slightly lateralized, ipsilateral to the pain side. No changes were seen comparing the two patient subgroups (in bout and out of bout). Seventeen of the patients were further investigated with PET, which showed activation in the very same area. The authors conclude that the observed changes were likely to be permanent and thereby specific to the disease, not merely a reaction of the brain to pain. They describe their finding as "the precise anatomical location for the central nervous system lesion of CH", hypothesizing that VBM may be capable of detecting brain lesions that remain unrecognized on conventional MRI.

The study was performed in the very early days of structural brain imaging, and from today's point of view there are methodological issues that the authors could not be aware of at that time. One example is the used software, which was significantly improved in the years after. Moreover, the control group was not precisely matched regarding gender and age. Both factors are known to considerably influence VBM results [36]. Furthermore, no information was provided as to whether global covariates were included into the statistical model, something that has become more and more recognized in recent years.

Work done at the Institute of Neurology, University College London, is only available as part of a PhD thesis [37]. Matharu investigated 66 patients with CH (19 females, mean age 46 years) and 96 healthy controls (23 females, mean age 43 years). He used the same 2 T MRI scanner used in the study before, but utilized a newer software version with optimized analysis technique (SPM99). A correction of multiple comparisons was applied and the significance threshold was defined at $p<0.05$. Additionally, small volume correction (SVC) for the hypothalamic area was conducted. Upon comparing CH patients with the matched controls, no alterations were seen regarding GM and WM. Matharu concluded that the initially observed hypothalamic alteration was likely to be an artifact due to methodological limitations, but admits that optimization in the VBM protocol might potentially have lowered the sensitivity of the technique so that the small area of the hypothalamus could not be detected. Most migraine- and tension-type-headache VBM studies used by far lower thresholds to detect GM changes and often did not correct for multiple comparisons [38–42]. In his manuscript, Matharu stressed the need for further studies and that the results cannot rule out biochemical dysfunction of the hypothalamus.

A more recent study was done by Absinta et al. [43•] and investigated 15 right-handed patients (two women, mean age=44 years) suffering from episodic CH in a pain-free state (out of bout) for at least a month at the time of recording. At the time of MRI none of the patients were on any particular treatment for the headaches. The control group consisted of 19 healthy volunteers (seven women, mean age=42 years). Tract-based spatial statistics (TBSS) and VBM were performed. Images were acquired using a 3 T machine. VBM was analyzed using SPM8 with modulation including "unified segmentation" and "DARTEL" [44, 45]. Similar to the study by May et al., regions showing abnormalities were reported with a threshold of $p<0.001$ (uncorrected). Patients suffering from CH showed significantly reduced GM volume of the right thalamus, the right posterior cingulate cortex, left inferior parietal lobe, the head of the right caudate nucleus, the bilateral middle frontal gyrus, the right-middle temporal gyrus, the right precentral gyrus and the left insula. Importantly, not only decrease but increase in the right cuneus was observed. Results were similar after hemisphere mirroring of the five patients with left-sided CH. No change within the hypothalamus was detected in this study.

The authors interpreted their results as GM "injury" in multi-integrative structures and concluded their findings to be in line with the other studies investigating chronic painful conditions. They highlighted the finding of GM decrease in the caudate nucleus, as there is evidence in the literature for the involvement of this structure in pain processing and its potential antinociceptive function [46, 47]. Additionally, a correlation of disease duration and GM volume in the left-middle frontal gyrus was described. The authors hypothesized that changes found may be a consequence of the repetitive painful stimuli due to CH attacks and emphasized the need for longitudinal investigations for further clarification.

The largest VBM-study published so far comes from Taiwan using a 1.5 T scanner in Taipei [48•]. Yang and colleagues scanned 49 episodic CH patients in bout (i.b.)> 1 week (11 females, mean age=35.7 years) and 49 matched controls (11 females, mean age=35.2 years). Twelve of the patients were scanned for a second time out of bout. Patients i.b. were on Lithium, Verapamil, and/or Triptans. Analysis was performed using modulation, SPM8-VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/), and SPM8 including DARTEL. In the analysis of global volumes, GM was reduced in the CH patients compared to controls. Inside bout patients showed reduced GM volume in the bilateral middle

frontal gyri, the left superior, and medial frontal gyri (corrected, $p<0.05$). These frontal GM reductions were consistent after mirroring to the affected headache side. No GM increase was found for this analysis. Using the same threshold, no changes were seen in a comparison of the 12 patients out of bout with the healthy controls. Reduction in the left-middle frontal gyrus was only identified in uncorrected analyses ($p<0.001$). In the longitudinal comparison of the 12 patients scanned twice, bout state showed GM increase in the left anterior cingulate, the insula, and fusiform gyrus (corrected). No changes were found in performed hypothalamic small-volume correction and correlation analysis.

The authors interpreted their results of the affected frontal lobe as a possible reflection of impairment of the descending pain modulation system during the bout period, and, thereby, as a possible component in the complex pathophysiology of the disease due to a limited recruitment of pain modulatory networks. They furthermore suggested that the GM increase i.b. compared to o.b. may represent neuroplasticity or compensation mechanisms as an attempt to increase or regain pain modulation performance during the bout period, and that morphometric changes may be dynamic, which could explain the different findings in comparison to the previous studies. The statements of this study regarding o.b. vs. controls are very limited.

The largest cohort investigated so far is only available as a preliminary abstract and was presented at the International Headache Conference in Berlin [49]. This is the only study decidedly investigating the different courses of disease, i.e., episodic CH in bout, episodic CH out of bout, and chronic CH. A total of 91 patients suffering from CH were compared to 78 age- and gender-matched healthy controls [49]. Additionally, subgroup comparison was performed. The study used VBM8 including modulation and DARTEL to detect distinct regional GM changes in different brain regions associated with central pain processing. Interestingly, the direction, location, and extent of observed GM alterations were dependent on the state of disease and appeared to be very dynamic in relation to changing pain state. As all other studies performed after 1999, this study was unable to detect hypothalamic changes in any group (CH vs. controls) and subgroup comparison (in bout, out of bout, chronic). In line with other chronic pain conditions [30], chronic CH showed predominant GM decrease in previously described brain areas associated with chronic pain. The acute pain state in bout (i.b.) showed a far more complex GM behavior with pronounced GM increase (including temporal, orbitofrontal, hippocampal and insular alterations), but GM decrease as well (e.g., somatosensory, supplementary motor areas, and temporal lobe). In general, the patients out of bout showed less marked GM alterations compared to the other groups. Table 1.

This study again showed that morphological alteration seem to be dynamic in CH in regard to the course of disease, which is supported by a study that used acute experimental pain and also found a GM increase [50].

Although, or maybe because VBM has been used for over 20 years in CH, it appears very difficult to break down all the different and partly contradictory results to one final conclusion. The major differences in the trials may be based on the (a) different protocols used (e.g., high thresholding combined with older VBM-protocols as done by Matharu) and (b) different patient cohorts studied (e.g., i.b., o.b , chronic CH, or mixed groups).

The first ever VBM in a primary headache disorder was the only one that was able to identify structural alterations in the hypothalamus, while all following studies that tried to replicate this finding failed in doing so. From today's point of view it remains puzzling why no alterations in other areas associated with pain processing were found in that pioneering study. There are three conclusions that can be drawn from all these results.

First is that GM changes can be of high dynamics and may thereby reflect the cortical plasticity of the brain in regard to repetitive and chronic pain. This especially accounts for CH, since the disease has its own dynamic.

Second is the hypothesis that a complex network dysfunction, including the malfunction of prefrontal pain modulatory areas, the basal ganglia, and other multisensory integrative regions, seems to contribute to the underlying pathophysiology of CH. The hypothalamus may or may not play a role within this network, but does not appear to fulfill the paramount part that was ascribed to it in the past.

And lastly, as nearly all authors mention, there is a clear need for further studies with well-defined patient cohorts and longitudinal designs.

Diffusion-Tensor Imaging / Tract-Based Spatial Statistics

Although VBM generally has the capability of white-matter analysis, due to its limited explanatory power in this regard, analysis is mainly used to identify GM alterations. A newer approach in white matter structural brain imaging is diffusion-tensor imaging (DTI), which uses diffusivity as a correlate of white matter fiber tracts. One central parameter estimated in those studies is the so-called fractional anisotropy (FA), a scalar value from zero to one in which a higher value expresses the restriction of diffusion towards one axis. Statistical analysis is realized using tract-based spatial statistics (TBSS).

In regard to CH, scientific evidence gathered with this technique is very limited. Only three studies using TBSS have been performed to date. All have significant methodological limitations and results are very contradictory. The work done by Absinta et al. [43•] was already described in the VBM section. The same cohort (15 patients vs. 19 controls) was used for a DTI/TBSS analysis using the fMRIB's diffusion

Table 1 Studies performed with structural brain imaging in cluster headache

Author/Study	Year/Journal	No. of Subjects/Controls	Modality/Software	Key findings/nnotation
May et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome	1999, Nature Medicine	25/29	VBM/SPM96	Bilateral GM increase in the posterior hypothalamus. Pioneer study, which inspired many pain researchers; High impact on pathophysiological concept of CH; Some methodological issues.
Matharu Functional and structural neuroimaging in primary headache disorders	2006, Unpublished data (PhD Thesis)	66/96	VBM/SPM99	No significant GM or WM alterations. Using a high threshold P<0,05 (corrected); a small volume correction for the hypothalamus was performed.
Naegel et al. Distinct regional grey matter volume reduction in different states of disease in cluster headache	2011-2013, Abstract only (in preparation)	91/78	VBM/SPM8 (incl. DARTEL)	GM alterations in specific pain-processing regions, which appear to be very dynamic with changing pain status of the disease. Supports a complex network dysfunction in CH pathophysiology. Largest patient cohort, published as abstract
Absinta et al. Selective decreased grey matter volume of the pain-matrix network in cluster headache	2012, Cephalalgia	15/19	TBSS & VBM/FMRIB & SPM8	GM decrease in the pain network and GM increase in the right cuneus in VBM. No alterations seen in TBSS Only patients outside bout were scanned; small study.
Yang et al. Altered gray matter volume in the frontal pain modulation network in patients with cluster headache	2013, Pain	49 i.b./ 49 12 pat. rescanned o.b.	VBM/VBM8 Toolbox, SPM8, incl DARTEL	GM volume reduction in frontal areas, (i.b.) interpret as insufficient pain modulation system as part of complex pathophysiology. GM increase i.b. in longitudinal analysis (ACC, fusiform gyrus, Insula) Large cohort with dynamic changes, but longitudinal and out of bout groups are very small.
Teepker et al. / Diffusion Tensor Imaging in Episodic Cluster Headache	2012, Headache	7/7	TBSS/Freesurfer 4.2+FSL 4.1.2	Widespread findings interpreted as “lesions” in cortical and subcortical areas involved in nociceptive/trigeminal processing Very small sample size
Szabo et al. White matter disintegration in cluster headache	2013, The Journal of Headache and Pain	13/16	TBSS/FSL 4.0	Very wide spread reduction of FA and increase of diffusivity, alterations showed a contralateral dominance. Small sample size
Wang et al. Reduction in hypothalamic 1H-MRS metabolite ratios in patients with cluster headache	2006, J. Neurol Neurosurg Psychiatr	47/21/16 CM	Magnetic resonance spectroscopy/NA	Reduction of hypothalamic N-acetylaspartate/creatine and choline/creatine quotients compared with healthy controls and chronic migraine patients Large patient cohort, no difference i.b. vs o.b.
Seifert et al. A Case-Control Study on Cortical Thickness in Episodic Cluster Headache	2012, Headache	12/12	whole-brain surface-based comparison of cortical thickness	Cortical thinning was found in the contralateral angular and precentral gyrus. Hints for disease-related plasticity Small cohort, new method with potential

Abbreviations: CH=cluster headache; i.b. = inside bout; o.b. = outside bout; VBM=Voxel-based morphometry; GM=grey matter; WM=white matter; TBSS=Tract-based spatial statistics; FA=fractional anisotropy

toolbox of FSL 4.1 (http://www.fmrib.ox.ac.uk). No significant changes in FA or mean diffusivity (MD) were found for corrected ($p<0.05$) and uncorrected ($p<0.05$) thresholds.

A study done by Teepker et al. [51] performed DTI and TBSS on a very small cohort with seven male episodic CH patents (mean age=43.14) and seven controls (mean age= 50.43). One patient was inside the active phase, whereas the other six were not. Pre-processing and statistics were done using FLS 4.1.2, Freesurfer 4.2, and Matlab. Flipping was performed. Analysis detected significant regional changes of FA ($p<0.0001$, corrected) in the brainstem, the thalamus, the internal capsule, the superior and inferior temporal region, the frontal lobe, the occipital lobe and the cerebellum. The authors interpreted their widespread findings as "lesions" in cortical and subcortical areas involved in nociceptive/trigeminal processing. Orbitofrontal changes were interpreted as involvement of the olfactory system and alterations of the sympathetic system were suggested. Unfortunately, this study has the major limitation of a very small sample size and the scientific conclusions that can be drawn from its results remain very limited. The authors proclaim that they found changes in the cerebral pain processing system ("pain matrix"), although important parts of it did not show alterations (e.g., ACC, insular, or dorsolateral prefrontal cortex).

The newest TBSS study comes from Hungary and investigated 13 patients in the "interictal period" and 16 controls [52]. More than half of the patients suffered from right- sided CH, and images were mirrored to the affected headache side. Using FSL 4.0 and a threshold of $p<0.02$ (corrected), the authors identified a very widespread reduction of FA (in most of the white matter pathways). Accordingly, the MD was increased in the regions of FA decrease, with emphasis on frontal, parietal, and temporal juxtacortical WM. The authors, furthermore, looked for axial diffusivity (AD) and augmented perpendicular diffusivity, which were increased in numerous regions as well. Interestingly, the alterations showed a contralateral dominance. This is in line with a previous functional imaging study, where more lateralized activation was seen [8]. The authors concluded that these changes are similar to those found in a migraine cohort, but more extensive. They further suggested these changes to be possible biomarkers, which could be used in clinical trials.

Taking the results of the three TBSS studies together, there is not much to extract in regard to pathophysiology. All studies predominantly compared CH out of bout with healthy controls. All three were conducted with very small patient cohorts. One was not able to show any changes, while the other two showed very widespread alterations all over the brain. A central problem with TBSS with some similarity to VBM is that a fixed relation between the estimated parameters and the specific tissue microstructure is not well validated [53]. Hence, the results have to be interpreted very carefully — especially since there are not many similarities between the three studies and the changes probably are not very specific for CH. There is need for further research in CH and methodology.

Other Structural Imaging Modalities

Magnetic resonance (MR) spectroscopy is an interesting method not used frequently in headache research so far. In episodic CH patients, proton MR spectroscopy was performed and identified alterations in the hypothalamic area. Both N-acetylaspartate/creatine and choline/creatine quotients were reduced compared with healthy controls and chronic migraine patients. The reduction was persisted even in patients out of bout [54, 55]. The authors concluded that the changes might be specific for CH and not an epiphenomenon of experienced pain [54].

A different, more recent study investigated cortical thickness in 12 men with episodic cluster headache out of bout and compared them to age and sex-matched healthy controls [56]. Data were acquired at 3 T. Cortical thinning was found in the contralateral angular and precentral gyrus. No correlation was found in regard to disease duration in these areas, but was seen in the primary sensory cortex. A potential role of the observed altered cortical structures in cluster headache pathogenesis was discussed, respecting that the changes may as well be a consequence of the disease. The correlation of the thickness of the somatosensory cortex with disease duration was interpreted as possible disease-related plasticity.

Conclusion

Structural brain imaging had a major influence on our pathophysiological model of CH today. Multiple different structural imaging modalities were used in the investigation of this rare condition. Descriptions of symptomatic forms of cluster-like headache are remarkable and show that lesions in different areas of the brain and even in the peripheral nervous system are capable of provoking a perfect mimic of CH. Even though the results of VBM studies on CH are very diverse and partly contradictory on superficial examination, they clearly point towards a complex network performance deficit in CH rather than a single defected structure. Additional evidence comes from the cortical thickness study. A central problem of the VBM studies published is that the plasticity of the adult human brain is completely underestimated, despite the excellent VBM studies performed on training and learning. CH may be a perfect model condition to study this plasticity due to its different disease conditions and associated pain states. More sophisticated studies (especially longitudinal designs) are needed to address this aspect properly.

Whether TBSS data are valid or not will be clarified in the future. Changes seen are very widespread and if something can be derived from the data so far, it is that in CH the whole pain modulatory network may be structurally affected.

Spectroscopy data point towards biochemical changes in the hypothalamus, indicating that this structure plays its role in the disease as well, but most likely not to the extent that was previously expected. Hence, deep-brain-stimulation of this structure is highly questionable—especially since, serendipitously, other less-invasive neurostimulation methods are available already or are on their way.

The evidence collected with structural brain imaging so far has enriched our knowledge of more complex pathophysiological mechanisms of the disease, but more research in this area is needed to understand the results that appear to be somewhat conflicting in different domains.

Compliance with Ethics Guidelines

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