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Review

PET Imaging in Huntington's Disease

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Abstract. To date, little is known about how neurodegeneration and neuroinflammation propagate in Huntington's disease (HD). Unfortunately, no treatment is available to cure or reverse the progressive decline of function caused by the disease, thus considering HD a fatal disease. Mutation gene carriers typically remain asymptomatic for many years although alterations in the basal ganglia and cortex occur early on in mutant HD gene–carriers. Positron Emission Tomography (PET) is a functional imaging technique of nuclear medicine which enables *in vivo* visualization of numerous biological molecules expressed in several human tissues. Brain PET is most powerful to study *in vivo* neuronal and glial cells function as well as cerebral blood flow in a plethora of neurodegenerative disorders including Parkinson's disease, Alzheimer's and HD. In absence of HD–specific biomarkers for monitoring disease progression, previous PET studies in HD were merely focused on the study of dopaminergic terminals, cerebral blood flow and glucose metabolism in manifest and premanifest HD–gene carriers. More recently, research interest has been exploring novel PET targets in HD including the state of phosphodiesterse expression and the role of activated microglia. Hence, a better understanding of the HD pathogenesis mechanisms may lead to the development of targeted therapies. PET imaging follow–up studies with novel selective PET radiotracers such as ^{11}C-IMA–107 and ^{11}C-PBR28 may provide insight on disease progression and identify prognostic biomarkers, elucidate the underlying HD pathology and assess novel pharmaceutical agents and over time.

Keywords: Huntington's disease, PET, striatum, putamen, cortex, dopaminergic, microglia, TSPO

HUNTINGTON'S DISEASE – AN OVERVIEW

Huntington's disease (HD) is an autosomal progressive neurodegenerative disease which is characterized by an expanded CAG repeat in the Huntingtin (HTT) gene on chromosome 4. HD manifests with behavioural changes and cognitive impairment and a movement disorder which is most commonly chorea. The expansion of mutant HTT eventually leads to selective degeneration in the striatal medium spiny neurons which receive dopaminergic projections from the substantia nigra and glutamatergic ones from the cortex. Post–mortem pathology studies in HD patients have shown marked atrophies in the caudate and putamen nuclei, enlargement of the lateral ventricles as well as atrophies to the cortex, thalamus, and substantia nigra to some extent.

HD is typically diagnosed in young adults at the age of 40 and to date no treatment is available to reverse the progressive decline of function caused by the disease, thus considering HD a fatal disease.

Several studies have investigated the role of a wide range of pharmaceutical agents in managing HD symptoms, including dopamine depleting agents, dopamine antagonists, benzodiazepines, glutamate antagonists, acetylcholinesterase inhibitors, dopamine agonists, anticonvulsants, and cannabinoids. Pallidal and subthalamic nucleus deep brain stimulation as well as

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restorative therapy with allogeneic fetal tissue have been tried treating HD individuals, however with inconclusive results.

Still, the exact role of mutant HTT in provoking functional decline in HD remains unknown. Little is known about the mechanisms that underlie the disease's progression and propagation and in addition, there is no available biomarker to monitor HD progression and assess experimental treatments. In this article, we have reviewed the findings from key Positron Emission Tomography (PET) studies in manifest and premanifest HD gene–carriers summarising their results and identifying new areas for further research.

POSITRON EMISSION TOMOGRAPHY IN NEUROIMAGING

PET is a functional imaging technique of nuclear medicine with wide applications in neurology. PET has been widely used in neuroscience research over the past years to investigate *in vivo* the pathophysiology of several neurological conditions including Parkinson's, Alzheimer's and HD. Brain PET enables three–dimensional visualisation of biological compounds available in the human brain. PET imaging requires a PET radioligand, which is a metabolically active compound labelled with a radioactive isotope and a PET–CT scanner, which is a tomography scanner sensitive to detect radioactivity. PET–CT scans are carried out on an outpatient basis. Each PET ligand has unique pharmacokinetics and characteristics and therefore unique applications in clinical imaging studies. A PET radioligand in brain PET is synthesised to cross the blood brain barrier and have high affinity to a specific biological compound. The PET radioligand is injected in the circulation of the examinee minutes after its production, while γ-rays are emitted from the decay of the radioisotope for a certain amount of time; eg. ^{11}C has a half–life of approximately 20 minutes, ^{18}F of 110 minutes, and ^{15}O of only two minutes. Acquired PET data are transformed to a PET workstation, where they are reconstructed combined with CT and structural MRI data in order to quantify global and regional distribution of the PET radioligand.

Brain PET imaging technology and radioligand synthesis have shown great progress over the past decades. Improvements in computer–based methodology have enhanced image resolution and quantification of PET data, while novel radioligands are more selective to the studied disease pathology. Continued research in multimodal imaging including PET–CT and PET–MR will improve our understanding of neurodegeneration and neuroinflammation, validate *in vivo* diagnostics, and may provide biomarkers to monitor disease–modifying therapies. Hence, the above advances will improve the use of PET in HD as a research and clinical tool to assess the integrity of neurotransmission, explore the mechanisms of underlying HD pathology and monitor disease progression.

PET TARGETS IN HD

Dopaminergic terminals

Dopaminergic neurons physiologically abound in the basal ganglia. Both presynaptic and postsynaptic terminals can be targeted through PET to assess dopaminergic function and thus reflect the integrity of the basal ganglia dysfunction in HD.

From a postsynaptic terminal approach, PET radioligands including ^{11}C-raclopride and ^{11}C-SCH23390 are specific to visualize the distribution of D2, D3 and D1, D2 dopamine receptors respectively. PET studies in humans have shown a decline of striatal postsynaptic D1, D2 and D3 receptors availability in manifest and premanifest HD individuals. Turjanski and colleagues were first to show that HD patients had reduced D1 and D2 binding in caudate and putamen more than 30% of the normal range [1]. In addition to manifest HD, premanifest mutation gene–carriers have shown a decline in ^{11}C-raclopride binding in the caudate and putamen compared to the normal range [2–8].

The ^{11}C-raclopride and ^{11}C-SCH23390 binding reductions in the striatum have been shown to negatively correlate with disease duration in HD individuals [9]. In fact, dopaminergic degeneration has been shown to occur early on during the progression of the disease also in premanifest cases. PET follow–up studies have shown that ^{11}C-raclopride binding reductions occur progressively in HD [3, 5, 8, 10] as well as in the premanifest HD [11]. The decreases in ^{11}C-raclopride bindings in caudate and putamen have been found to exceed the changes caused by atrophy, as measured by volumetric MR imaging [11].

The rate of decline in ^{11}C-raclopride binding has been shown to negatively correlate with disease duration [5] and that it may follow a linear [6], a non–linear [10] or biphasic [11] progression. Annual losses of ^{11}C-raclopride binding at premanifest HD have been found greater than in patients at risk of developing HD [10]. In addition, lower ^{11}C-raclopride binding in the putamen of premanifest HD gene–carriers

have been shown to correlate with the probability to phenoconvert; however, not with the rate of decline in ^{11}C-raclopride bindings [7].

The dopamine transporter (DAT) is a membrane–spanning protein highly expressed in presynaptic dopaminergic terminals. The DAT is responsible for the reuptake of dopamine from the synapse back into the cytosol. PET imaging with ^{11}C-β-CIT, which specifically binds to the DAT, has shown 50% reductions of DAT availability in the striatum of HD individuals relative to normal controls [9]. It has been therefore proposed that reduced DAT expression reflects either loss of presynaptic dopaminergic terminals or poor auto–regulatory feedback mechanisms.

Vesicular monoamine transporter–type 2 (VMAT2) is a protein responsible for transporting monoamines into synaptic vesicles. A PET study with ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), which binds selectively to VMAT2, showed reduced striatal binding of ^{11}C-DTBZ in all HD patients compared to normal range [12]. ^{11}C-DTBZ binding reductions in the striatum were more pronounced in the subgroup of patients with the akinetic–rigid phenotype compared to the choreiform one.

D1 binding reductions have been measured also in the cortex and thalamus of HD patients and were found to correlate with volume measurements of thalamus and temporal cortex as well as with low scores of selected cognitive tasks [7, 13]. Losses of ^{11}C-raclopride binding have been measured in temporal and frontal cortex as well as the amygdala in premanifest HD [5]. Thalamic involvement is demonstrated in premanifest and manifest HD also for D2 receptors [14].

Taken together, the findings of the above studies suggest that the dopaminergic terminals in the striatum and cortex get in a compromised state regardless of the actual atrophies noted in the basal ganglia as HD progresses. It is also proposed that the rate of HD progression varies among individuals and that it may be a weak index to predict the onset of HD symptoms.

Cerebral blood flow and glucose metabolism

PET with ^{18}F–fludeoxyglucose (FDG) has been widely used to target the glucose metabolism and cerebral blood flow. In HD, PET studies with ^{18}F-FDG and $H_2{}^{15}O$ [15] have shown an annual decrease rate across premanifest and HD individuals compared to normal controls, suggestive that hypometabolism occurs in HD and actually precedes the clinical manifestation [3, 11, 16, 17]. The areas which have been studied to be most affected are the striatum, frontal and temporal cortex.

An interesting study employed ^{18}F-FDG PET in HD patients who were divided clinically in two groups for fast and slow progression rate. ^{18}F-FDG follow-up PET showed lower glucose metabolism in frontotemporal and parietal cortex in the faster group compared to the slower one [18].

Striatal reductions of ^{18}F-FDG have been found to decline in premanifest HD over time similarly to the annual decline observed in ^{11}C-raclopride binding [3]. Nonetheless, in premanifest HD gene–carriers, the decreases in ^{18}F-FDG binding have been less great compared to the ones observed through imaging of dopaminergic terminals in HD [3, 11]. Another ^{18}F-FDG PET study looked into the decline of metabolic rate in premanifest HD, and suggested that greater losses of ^{18}F-FDG in caudate may contribute to a CAG–age approach for predicting disease's onset [17].

Network analysis of ^{18}F-FDG PET data has shown a significant HD–specific spatial characteristics covariance pattern characterized by progressive metabolic decline in cortical and striato–thalamic activity network [6, 8].

Hence, the above studies may suggest that glucose hypometabolism is progressive in both premanifest and manifest cases of HD gene–carriers. However, results from PET ^{18}F-FDG studies are inconclusive as to whether ^{18}F-FDG PET can be used to predict the time HD gene–carriers phenoconvert.

PET imaging of cerebral blood flow has been employed also to study the mechanisms underlying abnormal cognition in premanifest HD. SPM analysis of $H_2{}^{15}O$ PET data showed increased thalamic and cortical activation in premanifest HD gene–carriers compared to controls, during the performance of learning and execution motor tasks. Premanifest HD gene–carriers showed impaired learning performance but normal execution of motor tasks, suggesting that enhanced activation of thalamocortical pathways is perhaps compensating the striatal degeneration in premanifest HD [19].

In comparison to monoamines PET radioligands, it can be therefore proposed that glucose metabolism is indeed interesting in HD, however, may serve as a less robust index for assessing HD dysfunction and progression.

Cannabinoid system

The cannabinoid system has focused great research interest in several neurodegenerative disorders. A PET

study with ^{18}F-MK9470, which specifically binds to cannabinoid receptors–type 1 (CB1), looked into a cohort of 20 symptomatic HD patients and found a widespread reduction in the CB1 receptors availability relative to controls in the cortex, brainstem and cerebellum. However, no correlations were found between ^{18}F-MK9470 bindings and clinical unified Huntington's disease rating scale (UHDRS) motor scores, disease duration, and the CAG length [20].

Opioid system

PET imaging with ^{11}C–diprenorphine, which is a non–selective partial agonist for the delta, kappa, and mu opioid receptors, has shown reduced binding in the caudate and putamen in manifest HD patients relative to normal controls [21]. The above study is interesting also from a methodology point of view; the authors analysed the PET data using an ROI approach of static and dynamic data, spectral voxel approach of dynamic data and a group analysis of voxel-based parametric images using SPM. Among the different approaches, it was the results from dynamic time–activity curves which showed larger differences and greater significance.

PD10

Phosphodiesterase 10 (PD10) is highly expressed by the medium spiny neurons in the striatum and is believed to play a role in the dopaminergic and glutamarergic neurotransmission. In addition, in the animal model of HD, mutant HTT has been suggested to possibly downgrade the expression of PD10. PET imaging with ^{18}F-MNI-659, which specifically binds to PD10, has showed reduced ^{18}F-MNI-659 binding in the basal ganglia of HD individuals relative to controls [22]. Very recently, a PET imaging study with ^{11}C-IMA–107 which is a highly–selective PD10 radioligand, looked into a cohort of premanifest HD individuals who had further probability. The authors showed reduced ^{11}C-IMA–107 binding in the caudate, putamen and globus pallidus and increased binding in motor thalamic nuclei compared to controls, suggesting that PD10 alterations occur several years before the predicted development of symptomatic disease [23].

Further studies including larger numbers of participants and follow–up scans may suggest that PD10 PET imaging is a promising biomarker for monitoring HD progression as well as assess PD10–orientated treatments.

Microglia in HD

Recent studies on the role of microglia in HD have suggested that activated microglia may aggravate the pathology in HD and contribute to the propagation of the disease.

Microglia consist less than 10% of the cells in the human brain [24]. In physiological conditions, microglia remains in a resting state representing the main phagocytic cells of the human brain. Traumatic injury, ischaemia, central nervous system inflammation, and neurodegeneration lead microglia to proliferate, change morphology, gene expression and function which is defined as activated microglia [25].

However, activated microglia, besides being phagocytic cells, secrete several hazardous neurotoxins such as free radicals, nitric oxide, proteinases, and interleukines. Activated microglia may therefore cause neuronal damage and aggravate underlying pathology. In fact, mutant HTT expression in microglia has been linked to an increase in the expression of several inflammatory response genes [26].

In particular, activated microglia have been found in HD individuals in the caudate and putamen nuclei, the globus pallidus and cortical areas in all grades of pathology compared to controls [27]. In addition, the dysregulating role of activated microglia in HD has been supported by studies in the animal model of HD [28, 29].

Currently, PET imaging of microglia has developed PET radioligands which specifically bind to the translocator protein (TSPO). TSPO is an 18 kDa protein mainly found in the outer mitochondrial membrane, which translocates the cholesterol. TSPO is highly expressed in activated microglia compared to physiological microglia state. Quantification of TSPO binding is therefore believed to reflect the state of activated microglia.

An interesting PET study with the TSPO radioligand ^{11}C-(R)-PK11195 showed increased ^{11}C-(R)-PK11195 binding in the whole striatum and globus pallidum which correlated with striatal decreases in ^{11}C-raclopride binding. In addition, lower ^{11}C-(R)-PK11195 binding correlated with higher UHDRS scores [30]. The above results were explored further with ^{11}C-(R)-PK11195 PET in a group of premanifest HD gene–carriers. The striatal ^{11}C-(R)-PK11195 bindings of gene–carriers inversely correlated with ^{11}C-raclopride bindings. Moreover, higher striatal ^{11}C-(R)-PK11195 bindings correlated with higher probability [31] of HD diagnosis within five years [32]. ^{11}C-(R)-PK11195 increased bindings in the post-

Table 1
Summary table of key PET studies in Huntington disease (HD) studies

Short name of PET radioligand	PET radioligand target	Relevance to HD pathology	Utility for tracking disease progression in HD clinical trials.	References
Dopaminergic terminals				
^{11}C-raclopride	D2 and D3 dopamine receptors	Striatal medium spiny neurons receive dopaminergic projections from substantia nigra. Post mortem studies suggest degeneration of striatal medium spiny neurons in HD individuals.	Dopaminergic PET radioligands including ^{11}C-β-CIT and ^{11}C-raclopride have been useful to monitor progression in Parkinson's disease and could be used to monitor HD progression. Nonetheless, in HD, past clinical trials with dopaminergic medicines had inconclusive results for managing HD symptoms.	1–11, 13-14, 32, 34, 42, 44, 45
^{11}C-SCH23390	D1 and D2 dopamine receptors			1, 2, 9, 10, 13, 42, 44
^{11}C-β-CIT	Dopamine transporter			9, 13
^{11}C-DTBZ	Vesicular monoamine transporter–type 2			12
Cerebral blood flow and glucose metabolism				
^{18}F–FDG	Glucose metabolism	Non–specific to HD pathology.	Past PET studies in cerebral blood flow and glucose metabolism have been inconclusive as to whether PET imaging can detect time of clinical manifestation and monitor HD progression.	3, 6–8, 11, 16–18, 41–44, 46
$H_2{}^{15}O$	Cerebral blood flow			15, 19
Cannabinoid system				
^{18}F-MK9470	cannabinoid receptors–type 1 (CB1)	Post mortem studies suggest loss of CB1 protein in the basal ganglia of HD individuals.	Lack of evidence that modulation of the cannabinoid system can improve HD patients clinically and that ^{18}F-MK9470 PET imaging can be used to monitor HD progression.	20
Opioid system				
^{11}C–diprenorphine	δ, κ, and μ opioid receptors	Post mortem studies in HD have shown reduced striatal, nigral and pallidal engkefalin and dynorphin expression and loss of opioid receptors.	Lack of evidence that PD10A–orientated treatments can improve HD patients clinically.	21

Table 1
(*Continued*)

Short name of PET radioligand	PET radioligand target	Relevance to HD pathology	Utility for tracking disease progression in HD clinical trials.	References
			^{11}C–diprenorphine has favorable kinetics but is a less selective PET radioligand for imaging the opioid system.	
Phosphodiesterase 10 (PD10)				
^{18}F-MNI-659	PD10A	PD10A is highly expressed in striatal medium spiny neurons. Post mortem studies suggest degeneration of striatal medium spiny neurons in HD individuals. Animal studies suggest a direct effect of mutant Huntingtin protein on PD10A expression.	Lack of evidence that PD10A–orientated treatments can improve HD patients clinically. ^{11}C-IMA–107 has favorable kinetics and could be a potential PET ligand to assess the efficacy of PD10A–orientated drugs.	22
^{11}C-IMA–107	PD10A			23
Neuroinflammation – Microglia activation				
^{11}C-DAA1106	Translocator protein (TSPO)– microglia	Preclinical studies suggest that TSPO is highly expressed in activated microglia. Activated microglia has been shown that it may aggravate neurodegeneration and contribute to the propagation of several neurodegenerative diseases including HD.	Lack of evidence that microglia modulators can improve HD patients clinically. The rs6971 polymorphism of the TSPO gene has explained the different binding affinities of TSPO PET radioligands in normal controls. Among TSPO PET radioligands, ^{11}C-PBR28 has favorable kinetics and can differentiate between high, mixed and low affinity TSPO binders and may be useful to monitor HD progression.	39
^{11}C-(R)-PK11195				14, 30, 32–34, 37
^{3}H-PK11195	TSPO – microglia			35–40
^{11}C-PBR28	TSPO – microglia			

central gyrus have been also found to strongly correlate with peripheral cytokine expression [33]. In addition, substantial microglia activation in regions related to cognition have been suggested to predict disease onset [34].

The above studies suggest that neuroinflammation alterations in microglia, as reflected by TSPO PET, occur in HD starting early on until the clinical manifestation. From a neuroinflammation point of view, PET imaging with TSPO radioligands can be therefore most powerful to assess the role of activated microglia in HD and assess treatments which target the modulation of neuroinflammation.

DISCUSSION AND CONCLUSION

PET imaging can provide robust evidence for assessing the efficacy of novel therapeutics in HD, notwithstanding that some limitations apply.

PET imaging of dopaminergic terminals seems to stand as a significant index of visualising neural dysfunction in the striatum, which is among the mostly affected areas in the HD brain. A reasonable number of studies have used dopaminergic PET imaging to correlate their findings to clinical data relative to other PET radioligands including ^{18}F-FDG and TSPO ones. Nonetheless, imaging of dopaminergic terminals do not represent HD–specific pathology. In addition, past clinical trials in humans with dopaminergic medicines have had inconclusive results.

Similarly, PET imaging of glucose metabolism may have widespread applications; however, does not suffice to represent HD fully. The imaging of cannabinoid system is indeed interesting, however, there is a lack of evidence that modulation of the cannabinoid system can improve HD patients clinically. Striatal ^{11}C-diprenorphine decreases observed in HD were less great compared to the ones in dopaminergic PET imaging studies. It could be therefore suggested that the opioid receptors are relatively preserved in the striatum through the course of the disease.

Besides the above approaches, PD10 PET studies may provide a better understanding of the role of mutant HTT. Hence, PD10–orientated treatments may show significant results in managing HD symptoms and in this view, PD10 PET can be a promising radioligand for future PET studies.

From a neuroinflammation point of view, previous TSPO radioligands including the ^{11}C-(R)-PK11195 have been limited in research imaging studies by second generation TSPO PET radioligands including the ^{11}C-PBR28 which has favorable kinetics and greater signal-to-noise ratio than ^{11}C-(R)-PK11195 [35–38]. In humans, the ^{11}C-PBR28 binding to TSPO has different affinities in the general population, which is shared among all tested second generation TSPO radioligands including ^{11}C-DAA1106. Owen and colleagues [39], demonstrated that the different affinity is caused by the rs6971 polymorphism on the TSPO gene resulting in three patterns of TSPO binding [40]. Subjects without the polymorphism have high affinity for ^{11}C-PBR28, homozygotes have low affinity binding, while heterozygotes express mixed affinity binding. Low affinity binders are easily identified by PET due to negligible ^{11}C-PBR28 binding *in vivo*. In this view, current TSPO PET radioligands are quite promising for visualising the state of microglia activation. TSPO is therefore not meant to be a diagnostic target for imaging in HD, but a potential biomarker for imaging HD progression.

PET imaging can be used to monitor and assess results from restorative therapy trials [41–46] by targeting function of dopaminergic terminals and cortical metabolic rates. Fetal transplantation trials showed stability of grafted tissue post–transplantation. However, results from the above studies have been inconclusive for restoring and maintaining striatal function in HD individuals. PET studies with larger numbers of participants and multi–modal imaging including MR imaging may provide greater robustness to future restorative studies.

Notwithstanding, the exact mechanisms underlying glutamatergic dysfunction of medium spiny neurons in HD, to our knowledge, glutamatergic neurotransmission has not been studied through PET in HD individuals. In that sense, *in vivo* imaging of glutamatergic function may improve significantly our understanding of HD pathophysiology.

Nonetheless, design of PET radioligands for imaging glutamatergic neurotransmission is challenging. Type 1 of the metabotropic glutamate receptors' (mGlu1) availability has been proposed to decrease in the rodent model of HD [47] but not that of type 5 (mGlu5). Several agents have been designed as PET radioligands for visualising mGlu1 distribution; nonetheless, many have been shown to share similar characteristics for the different mGlu subtypes and unfavorable PET imaging kinetics. Among these, ^{11}C-LY2428703, ^{11}C-ITMM, and ^{11}C-ITDM have been shown to have a good affinity for mGlu1 in preclinical studies, however, in humans, ^{11}C-LY2428703 uptake was quite poor [48], while ^{11}C-ITMM had the lowest uptake in the cortex and the striatum

[49]. ^{11}C-ITDM has been studied in the rodent model of HD [50] demonstrating an mGlu1 receptors' decrease in the striatum; yet these findings have not been reiterated with PET in humans. PET imaging with ^{18}F-FIMX showed favourable kinetics and high cerebellar distribution of mGlu1 in the human brain; nonetheless thalamic and caudate distribution of mGlu1 were moderate and low, respectively [51]. Hence, PET with ^{18}F-FIMX may indeed prove useful to assess glutamatergic neurotransmission; however perhaps less powerful to detect striatal dysfunction in HD.

The most studied ionotropic glutamate receptors in relation to HD refer to N-methyl-D-aspartate (NMDA) receptors. The function of NMDA receptors appears to be altered in HD and related to toxic consequences in neurons, induced by pathological excitatory glutamatergic neurotransmission. NMDA binding sites have been demonstrated to decrease hugely in the insula and the putamen among HD individuals [52] and in that sense, NMDA PET radioligands could be useful to assess striatal and cortical dysfunction in HD.

Several novel PET radioligands have been developed targeting NMDA receptors binding sites in preclinical [53] as well as in studies in humans including ^{11}C-CNS5161 [54, 55] and ^{18}F-GE-179 [56], which show favorable kinetics in the human brain.

Further research with novel highly selective glutamatergic PET radioligands in HD may provide a better understanding of the basal ganglia glutamatergic dysfunction and may show evidence for the development of novel therapeutics.

PET imaging can therefore apply in assessing alterations before and after experimental treatments including novel neuromodulating compounds and invasive restorative therapy.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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