J Neural Transm (2011) 118:673–681
DOI 10.1007/s00702-011-0594-9

DEMENTIAS - REVIEW ARTICLE

MRI-detected white matter lesions: do they really matter?

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Received: 8 October 2010 / Accepted: 27 January 2011 / Published online: 22 February 2011

Abstract Despite extensive research over the last decades the clinical significance of white matter lesions (WMLs) is still a matter of debate. Here, we review current knowledge of the correlation between WMLs and cognitive functioning as well as their predictive value for future stroke, dementia, and functional decline in activities of daily living. There is clear evidence that age-related WMLs relate to all of these outcomes on a group level, but the inter-individual variability is high. The association between WMLs and clinical phenotypes exists particularly for early confluent to confluent changes, which are ischaemic in aetiology and progress quickly over time. One reason for the variability of the relationship between WMLs and clinic on an individual level is probably the complexity of the association. Numerous factors such as cognitive reserve, concomitant loss of brain volume, and ultrastructural changes have been identified as mediators between white matter damage and clinical findings, and need to be incorporated in the consideration of WMLs as visible markers of these detrimental processes.

Keywords Magnetic resonance imaging · MRI · White matter lesions · Cognition · Dementia

This article is dedicated to Professor Kurt Jellinger in admiration of his outstanding research achievements in the field of dementia and in appreciation of his long-standing support for our research group.

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Abbreviations

AD	Alzheimer's disease
ADAS	Alzheimer's disease assessment scale
ARIC	Atherosclerosis risk in communities
DM II	Diabetes mellitus type 2
CDR	Clinical dementia rating (scale)
CASCADE	Cardiovascular determinants of dementia (study)
LADIS	Leukoaraiosis and disability (study)
MCI	Mild cognitive impairment
MEMO	Memory and morbidity in Augsburg elderly (study)
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
PROSPER	Prospective study of Pravastatin in the elderly at risk
SMART-MR	Second manifestations of ARTerial disease-MR substudy
WMH	White matter hyperintensities
WML	White matter lesions

Introduction

The prevalence of white matter lesions (WMLs) in the general population is common. It increases steadily with age and the majority of subjects above the age of 75 years are affected (de Groot et al. 2000). WMLs have been consistently related to vascular risk factors (Longstreth et al. 1996; Schmidt et al. 2000); but despite extensive research, their clinical importance is still debated. Thus, it is not surprising that clinicians often struggle to explain to their patients the implications of these MRI findings. Here, we summarize current results on the association between WMLs and cognitive functioning, and discuss their role as predictors of stroke and disability. We address the issue of different lesion types and their relation to clinical findings, and seek to explain the large variability in the clinical presentation of individual subjects with WMLs.

WML types

White matter lesions are best visualized by fluid-attenuated inversion recovery (FLAIR) sequences, which have the advantage of suppressing cerebrospinal fluid (CSF) signal and thus allow for high contrast lesion delineation even at periventricular or perisulcal locations. FLAIR also enables a simple distinction between WML and lacunes as the core of lacunes is typically of CSF-like appearance. Most MRI-rating scales distinguish between WMLs in periventricular and deep/subcortical regions, and grade the respective changes separately (Kapeller et al. 2003). Both regions contain not only small vessel disease-related but also non-ischaemic changes (Fazekas et al. 1991, 1993). In the periventricular area, non-ischaemic changes are also called "caps", "lining", and "bands" or a "halo" of high T2 signal (Fig. 1). They reflect only mild pathology in the 5–10 mm zone directly adjacent to the ventricles. Disruption of the ependymal lining, myelin pallor, and some subependymal astrogliosis are histopathological correlates. In the deep and/or subcortical white matter, one can distinguish between "punctate", "early confluent", and "confluent" WMLs. Per definition "punctate" WMLs are single lesions <10 mm and/or areas of "grouped" lesions <20 mm in any diameter; "early confluent" WMLs are hyperintense lesions 10–20 mm linked by no more than "connecting bridges" or single lesions >20 mm in any diameter; while "confluent" WMLs represent widespread hyperintense areas of >20 mm in any diameter which show clear confluency between abnormalities. Early confluent abnormalities tend to progress to confluent lesions over time.

Punctate changes can result from a number of often non-ischaemic aetiologies including widening of perivascular spaces or even heterotopia of ganglionic cells (Fazekas et al. 1991, 1993). In contrast, early confluent and confluent changes in the deep but also in the periventricular white matter are clearly related to small vessel disease. They mostly relate to extensive demyelination and axonal loss, which may or may not contain small cavities of tissue destruction (Fig. 2).

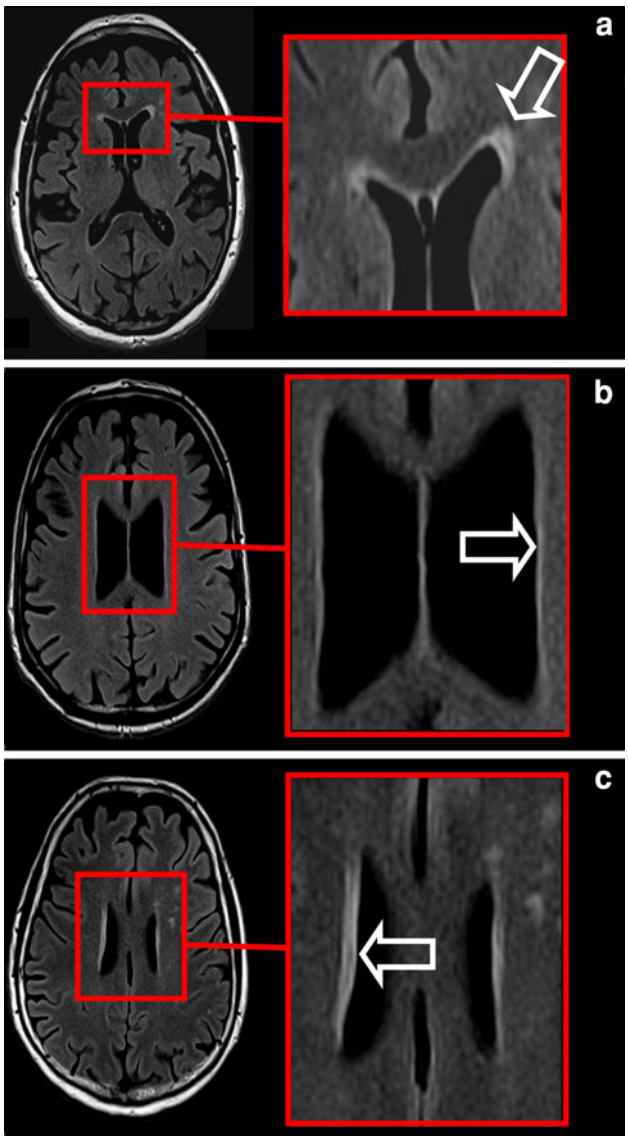

Fig. 1 Periventricular signal hyperintensities as seen on FLAIR-weighted MRI scans of the brain in axial orientation at 3T. *Arrows* in *enlarged insets* show caps (**a** 77-year-old female), pencil-thin lining (**b** 76-year-old male), and halo (**c** 56-year-old female)

In line with these pathological findings, the Austrian Stroke Prevention Study has shown that punctate lesions remain stable over time, while participants with a baseline finding of early confluent or confluent changes showed a remarkably rapid increase in lesion volume (Schmidt et al. 2003). Almost two-thirds of study participants with early

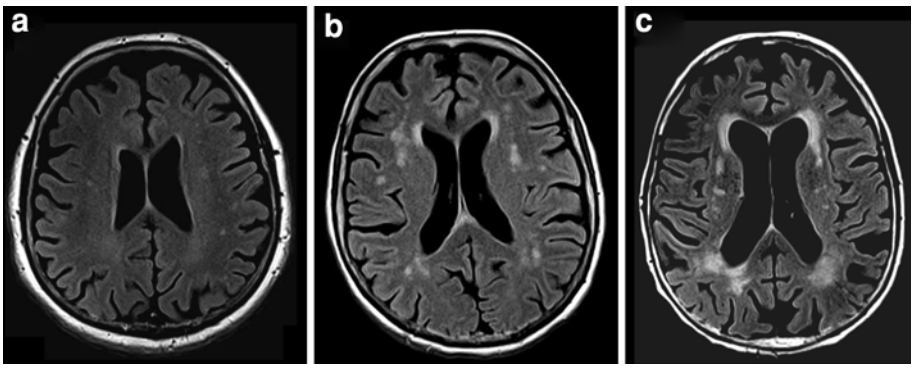

Fig. 2 Deep white matter hyperintensities (WMH) as seen on T2-weighted FLAIR MRI scans of the brain in axial orientation at 3T. Punctate (**a** 77-year-old female), early confluent (**b** 66-year-old male), and confluent WMH (**c** 78-year-old-female)

confluent and all subjects with confluent lesions demonstrated progression beyond measurement error over 6 years, while this was seen in none of the subjects with a normal baseline MRI scan and in only 14% of those with punctate foci. Clinical correlates are in keeping with these data as all studies consistently demonstrated an association between progression of leukoaraiosis and cognitive decline, with individuals who had coalescent white matter damage declining the most (Garde et al. 2005; Schmidt et al. 2005; van den et al. Heuvel 2006).

Therefore, histopathological, radiological, and clinical evidence clearly indicates that punctate WMLs are probably of mixed origin and rather benign, while early confluent and confluent WMLs are ischaemic, progressive, and thus malignant. Progression of WMLs was also demonstrated in subjects with dementia of various aetiologies but from these small studies no indication can be derived for an influential effect on the dementing illness per se. Progression rates were again influenced primarily by the severity of lesions at baseline rather than by the type of dementia or cognitive decline (Burton et al. 2006).

A recent investigation showed that progression of leukoaraiosis occurs throughout the brain but with some regional variation. The increase in deep WML volume was greater than that seen in the periventricular white matter. Frontal lesions progressed the most and occipital lesions the least (Sachdev et al. 2007).

Cognitive impairment, cognitive decline, and dementia

There is ample evidence that WMLs are associated with deficits in executive function, often affecting activities of daily living, which result from erroneous goal formation, planning, and organization. Abstract reasoning is also commonly affected, but patients have only mild memory deficits with slight recognition and cueing difficulties. A summary of cross-sectional studies on this topic conducted over the last decade is given in Table 1. As can be seen from this table, the studies were done in both community- and hospital-based cohorts with largely varying sample sizes and neuropsychological test batteries. Besides these differences, some cognitive impairment has been reported in all but one small investigation (Ross et al. 2005), and effects on cognition were seen in community-dwelling subjects as well as in individuals suffering from mild cognitive impairment and Alzheimer's disease.

Importantly, several studies in population-based samples reported WMLs to be related not only to cognitive impairment but also to cognitive decline (Prins et al. 2005; Schmidt et al. 2005). Similar results have also been described in high-risk populations, with executive dysfunction and speed of mental processing declining the most (Longstreth et al. 2005; Kramer et al. 2007; Van Dijk et al. 2008).

A recent meta-analysis showed WMLs to independently predict dementia in the general population, and this was seen for both incident vascular dementia and Alzheimer's disease (Debette and Markus 2010). However, the relation to incident Alzheimer's disease was driven by a single large population-based study (Kuller et al. 2003), whereas smaller studies in patients with mild cognitive impairment did not identify significant associations (Debette and Markus 2010).

When summarizing the findings of previous investigations, WMLs seem to have subtle but noticeable cognitive consequences, which very likely result from frontal–subcortical circuit involvement (Schmidt et al. 2006). First evidence from functional MRI indirectly supports this notion (Linortner et al. 2010). However, so far, the mechanisms by which white matter damage predicts dementia have not been fully determined, although interactive effects with Alzheimer pathology are likely to play an important role (Zlokovic 2005).

Another suggested mechanism responsible for the association between WMLs and incident dementia is amyloid angiopathy, which is frequently seen as part of the spectrum of Alzheimer pathology. In such cases, it is likely atrophy precedes the development of WMLs rather than follows it. We investigated this question in a small

Table 1 Clinical correlates of white matter lesions on the group level

Reference	Study population	*N*	Main findings relating WML and cognition
Bracco et al. (2005)	Probable AD, longitudinal survey	86	Periventricular WMLs are associated with executive function
Burns et al. (2005)	Non-demented, very mild and mild AD	156	WMLs related to global cognition in AD; no relation in non-demented
Mosley et al. (2005)	ARIC cohort (individuals aged 55–72, population-based)	1,538	High-grade WMLs related to all cognitive measures
Mungas et al. (2009)	Persons recruited by the UC Davis Alzheimer's Disease Center, African Americans, Hispanics and Caucasians, 60 years and older	1,219	WMLs in all ethnic groups related to episodic memory and executive function
Price et al. (2005)	Outpatients who met criteria for Dementia	69	Decline in executive functions and visuoconstruction
Prins et al. (2005)	Prospective, population-based Rotterdam Scan Study	832	Small vessel disease affects information processing speed and executive function
Ross et al. (2005)	Subjects with WML findings at MRI out of 257 scans	31	Leukoaraiosis not related to any of the cognitive or behavioural assessments
Sachdev et al. (2005)	Subsample of persons aged 60–64 from a larger community sample	478	Related to slowed information processing speed but not other cognitive functions
Shenkin et al. (2005)	Community-dwelling, mean age 78.4 years	105	WMLs correlate with poorer cognitive function (MMSE)
Söderlund et al. (2006)	CASCADE (community-dwelling), mean age 69.4 years	1,254	WMLs predicted lower performance in word fluency and the Stroop test
van der Flier et al. (2005)	LADIS	581	Severe WMH associated with non-significant increase in frequency of mild cognitive deficits
van der Flier et al. (2005)	LADIS	633	WMLs associated with MMSE score and ADAS score
Au et al. (2006)	Framingham Offspring Cohort, dementia- and stroke-free	1,820	Large WMH volume related to poor performance in cognitive domains generally associated with frontal lobe systems (visuospatial memory and organization, visual scanning, motor speed and new learning)
Chen et al. (2006)	AD, MCI, and controls	56	Boston Naming Test scores negatively correlated with WMH
van den Heuvel et al. (2006)	Subjects of the PROSPER study	554	Periventricular WMH associated with reduced mental processing speed
Sonohara et al. (2008)	Japanese elderly patients with mild cognitive decline, depression and low vitality	286	WMLs associated with cognitive impairment
Pohjasvaara et al. (2007)	Consecutive patients aged 55–85 years after ischaemic stroke	395	WMLs associated with global cognitive function, impaired memory functions and executive dysfunction
Rabbitt et al. (2007)	Healthy people, 61–85 years	133	WMLs associated with speed and executive function
Stenset et al. 2008	Patients with Global Deterioration Scale scores $\geq$3 with memory complaints	253	Subcortical WMLs associated with reduced cognitive function
Heo et al. (2009)	Korean patients with AD, mean age 65.7 years	142	WMH associated with score of MMSE and CDR
Debette et al. (2007)	Consecutive MCI patients	170	WMH, especially periventricular hyperintensities, associated with cognitive decline
Baune et al. (2009)	Participants aged 65–83 years of the population-based MEMO study	268	Large WMLs associated with impairment in multiple cognitive domains
Delano-Wood et al. (2008)	Older adults with MCI	70	Deep WMLs associated with executive impairment, slowed processing speed, and visuospatial/ construction difficulties and overall poorer neuropsychological functioning
van Harten et al. (2007)	Patients with DM II, mean age 73.2 years	92	Periventricular WMLs associated with motor speed, deep WMLs not associated
Koga et al. (2009)	Non-demented elderly Japanese, average age 72.4 years	350	WMLs associated with diffuse cognitive decline

Table 1 continued

Reference	Study population	*N*	Main findings relating WML and cognition
Zhou et al. (2008)	Non-demented Chinese veteran cohort	611	Severe WMLs associated with impaired cognitive function
Muller et al. (2009)	Patients with atherosclerotic disease from the SMART-MR study	605	Interactive effects of WMLs with brain volume on executive performance
Tiehuis et al. (2008)	Participants of the Utrecht Diabetic Encephalopathy Study	154	WMH associated with information processing speed, attention and executive function
Geerlings et al. (2009)	Patients of SMART-MR study	522	WMLs associated with worse executive functioning, not associated with memory

subgroup of a study on the relationship between the longitudinal change in WMLs and brain atrophy, and their interactive effects on cognition (Schmidt et al. 2005). A small subgroup of study participants had no brain atrophy but extensive white matter changes at baseline. This subgroup experienced a substantially greater loss of brain volume during subsequent years than their counterparts without white matter foci. This supports the view that WML progression precedes loss in parenchymal volume in non-demented elderly subjects, but longitudinal data in larger samples are needed to better understand the temporal relationship between subcortical small vessel disease, cerebral atrophy. and their effects on cognitive functioning.

Incident stroke

White matter lesions have been repeatedly found to predict future strokes in high-risk groups but also in the general population (Wong et al. 2002; Vermeer et al. 2003; Kuller et al. 2004; Fu et al. 2005; Naka et al. 2006). In all studies, the association of WMLs with stroke remained significant after adjustment for vascular risk factors, which suggests either that WMLs reflect the overall effect of uncontrolled vascular risk factors better than the mere presence or absence of each individual factor or that other, yet unknown, factors play a role in the association between WMLs and stroke.

Functional decline in activities of daily living

The LADIS study has shown that despite independent everyday-life activities at baseline, subjects with WMLs developed functional impairment in activities of daily living at 1 year (Inzitari et al. 2007) and even more pronounced at three years follow-up (Inzitari et al. 2009). The study used Lawton and Brody's (1969) instrumental activities of daily living scale and defined the change from a score of 0 or 1 at baseline to a score of 2 or more as the primary endpoint. These findings are important as they clearly demonstrate that deficits related to WMLs are not only detectable by demanding neuropsychological test batteries but also affect daily-life functions.

Clinical correlates of WMLs on the individual level

The high prevalence of WMLs in older populations and the large inter-individual variability of the clinical presentation of subjects with such abnormalities make clinicians uncertain whether WMLs are actually important and how to explain their clinical meaning to patients. In a study by Garde and co-workers (2000), WMLs only partly accounted for the inter-individual differences of age-related cognitive decline. Although cognitive dysfunction related to WMLs is most likely influenced by their distribution in strategically relevant brain regions and their volume (Desmond 2002), it is still unclear which locations are crucial and if there is a threshold of lesion volume which consistently leads to substantial cognitive impairment or dementia.

In a study on mixed dementia, Jellinger and Attems (2007) described that a vascular lesion volume smaller than 10 ml in manifest AD does not further influence cognitive impairment, unless strategically located infarcts occur. Their data are in favour of a complex interplay between location and volume influencing the cognitive phenotype of individuals with white matter disease. Another factor that is likely to be responsible for inter-individual variability of the cognitive consequences of WMLs is cognitive reserve, an issue that has remained virtually unappreciated in research on small vessel disease, so far. There is only one study suggesting that complex cognitive leisure activity exerts interactive effects with WML load on cognitive functioning in the general population (Saczynski et al. 2008).

WMLs, ultrastructural changes, and cognition

Diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) are currently the two most promising techniques for a more direct assessment of the composition

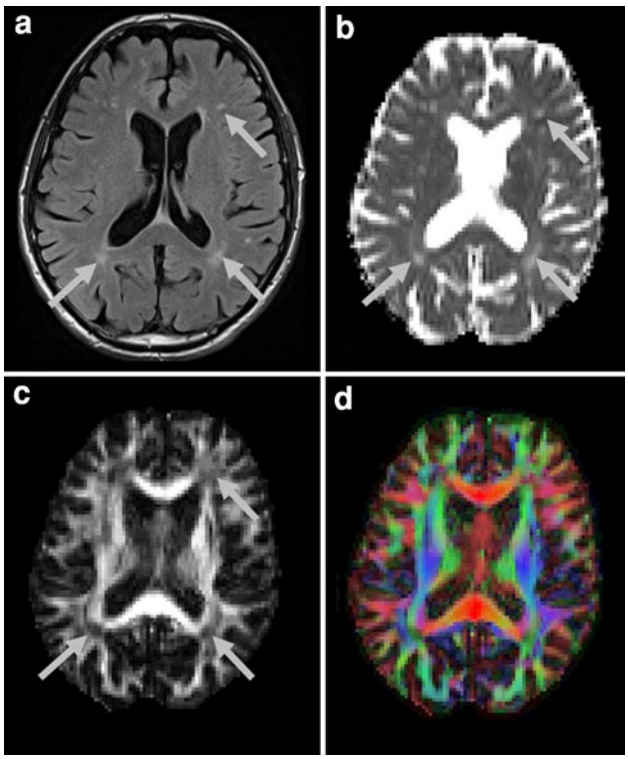

Fig. 3 **a** Fluid attenuation inversion recovery, **b** mean diffusivity, **c** fractional anisotropy and **d** directional colour-coded fractional anisotropy images of a 66-year-old male subject at 3T. Maps **b–d** are derived from a diffusion tensor imaging (DTI) sequence using 12 diffusion gradient directions. DTI allows to quantitatively assess the mean water diffusivity at each voxel (**b**) as well as fractional anisotropy values as a measure of tissue integrity (**c**). By colour-coding, the principle Eigen-vector of the DTI data the principal fibre direction can be visualized (**d**) (e.g. fibres of the corticospinal tract running in *z*-direction shown in *blue*, fibres of the corpus callosum in the *x–y* direction shown in *red*). *Arrows* indicate confluent and punctate white matter lesions in the posterior and frontal white matter, respectively (**a**). Mean diffusivity in white matter lesions is increased probably due to demyelination (**b**) and this is paralleled by a loss of fractional anisotropy values as an indicator of impaired tissue integrity. Different *shades of gray* in **c** represent different magnitude of altered tissue integrity, while **d** indicates the predominant direction of fibres both in lesions and normal-appearing brain tissue

and integrity of white matter structures. DTI and MTI have been used as tools to explain impaired cognition in individuals with WMLs beyond what can be expected from lesion volumetry alone (Fig. 3).

It is hypothesized that, in subjects with age-related WMLs, an increase in the apparent diffusion coefficient occurs not only in areas of T2 hyperintensity but also in normal-appearing white matter. In line with this assumption, it was shown that mean diffusivity of normal-appearing white matter is more closely related to clinical deficits than the volume of visible white matter damage. Two studies (Vernooij et al. 2009; Schmidt et al. 2010) corrected the association between diffusion imaging variables and cognitive functioning for both WML load and brain atrophy, and consistently found that diffusivity in normal-appearing white matter remained more strongly related to cognition than lesional volume and global brain atrophy.

Less data are available for MTI. Wong et al. (1995) found lower magnetization transfer ratio (MTR) values in periventricular brain regions compared with normal white matter. Our own group described the MTR of WMLs to be significantly lower than that of normal-appearing white matter and found a significant decrease with increasing lesion severity. The MTR of normal-appearing white matter was not different between subjects with very few and extensive WMLs. WML volume was associated with lower normal-appearing white matter MTR of the frontal lobes, but the MTR in frontal normal-appearing white matter was only related to fine motor dexterity but not to cognitive performance (Fazekas et al. 2005). These data are contrasted by work from Hanyu et al. (1999) who found correlations between the MTR values of age-related WMLs and cognitive functioning. It is important to emphasize that the pathological correlates of altered diffusivity and MTI measures are not yet fully determined. There is evidence that fractional anisotropy and mean diffusivity correlate directly with the amount of myelin in the white matter and to a lesser extent also with axonal count (Schmierer et al. 2007). Nonetheless, there is a need for more studies exploring the ultrastructural correlates of changes in the apparent diffusion coefficient and MTR to gain more insight into what histopathological abnormalities in the normal-appearing white matter can be picked up by either of the two methods. At this point, DTI appears to be more sensitive for tissue changes within WMLs and more robust for multicenter settings (Ropele et al. 2009).

Conclusions and future directions

Early confluent to confluent WMLs are related to cognitive decline, stroke, and functional decline in activities of daily living. Large, probably multi-centric collaborative efforts are needed to fully determine the threshold of WML load and strategically relevant locations that unequivocally lead to the different clinical phenotypes related to WMLs on a group level. Currently, the reasons for large inter-individual variability in the clinical presentation of subjects with WMLs are widely undetermined. Ultrastructural tissue changes that obviously occur in normal-appearing white matter in association with WMLs and other consequences of small vessel disease are at least partly responsible for inter-individual differences in the clinical picture in subjects with similar WML load. Histopathological post-mortem correlations together with the application of new imaging techniques in animal models of small vessel

disease, which at this point are only sparsely available, are likely to increase our understanding of the whole spectrum of WML-related brain damage.

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