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Differential Effects of Aging in the Macular Retinal Layers, Neuroretinal Rim and Peripapillary Retinal Nerve Fibre Layer

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Abstract

Objective: We determined the differential aging effects of the inner six layers of the macula in contrast to the minimum neuroretinal rim width (MRW) and peripapillary retinal nerve fibre layer (RNFL) thickness.

Design: Cross-sectional, multi-centre study.

Participants: Approximately equal number of White subjects with a normal ocular and visual field examination in each decade group from 20-90 years.

Methods: Optical coherence tomography of the macula, optic nerve head and peripapillary retina.

Main Outcome Measures: (i) Sectoral measurements of the inner six layers of the macula; (ii) age-related decline of each of these layers; (iii) strength of the associations with age of the macular parameters, MRW and peripapillary RNFL thickness; (iv) association between ganglion cell layer (GCL) thickness and MRW and peripapillary RNFL thickness.

Results: The study sample comprised one eye of 246 subjects with median (range) age of 52.9 (19.8 – 87.3) years. Of the six layers, there was a statistically significant decline with age of only the GCL, inner plexiform layer and inner nuclear layer thickness with rates of $-0.11 \mu\text{m/y}$, $-0.07 \mu\text{m/y}$ and $-0.03 \mu\text{m/y}$, respectively. These rates corresponded to 2.92%, 2.15% and 0.88% loss per

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decade, respectively, and were generally uniform across sectors. The rate of loss of MRW and peripapillary RNFL thickness was $-1.22 \mu\text{m}/\text{y}$ and $-0.20 \mu\text{m}/\text{y}$, corresponding to 3.63% and 2.04% loss per decade. However, the association of GCL thickness change with age ($R^2 = 0.28$) was approximately twice that of MRW and RNFL thickness ($R^2 = 0.14$ for each).

Conclusions: In concordance with histopathological studies showing age-related loss of retinal ganglion cell axons, we showed a significant decline in GCL thickness, as well as MRW and peripapillary RNFL thickness. The stronger relationship between aging and GCL thickness compared to the rim or peripapillary RNFL may indicate that GCL thickness could be better suited to measure progression of structural glaucomatous loss.

The retina is a highly laminated constituent of the central nervous system that is frequently studied in clinical and neuroscience research. It is the only part of the central nervous system that can be imaged optically with non-invasive methods; for example, optical coherence tomography (OCT), now used routinely in ophthalmic clinical practice, offering axial resolution in the range of 3-6 microns.¹ Assessing retinal structure by imaging remains an important component of detecting optic nerve and retinal diseases, gauging disease progression, and the efficacy of treatment interventions.

The interaction between aging and neurodegenerative disorders, such as Parkinson's² and Alzheimer's³ disease is widely acknowledged. Neurodegenerative diseases of the eye are no exception. In addition to the exponentially increased prevalence of age-related macular degeneration⁴ and glaucoma⁵ with age, there is persuasive clinical evidence, for example, that the phenotype of aging parallels that of glaucoma. The spatial patterns of structural alterations that occur in the optic nerve head (ONH) with aging and glaucoma are similar, albeit of greater magnitude in glaucoma.^{6, 7} More recent evidence with OCT imaging indicates that the rate of structural change in glaucoma, as measured by the ONH minimum rim width (MRW)⁸ and the retinal nerve fibre layer (RNFL)^{9, 10} has a significant aging component. Indeed, progression of these parameters, previously typically attributed only to glaucoma, can be explained in large part by aging as there was a lack of a statistical difference among treated glaucoma patients and healthy controls in the rates of MRW or RNFL thickness change.⁸

Retinal neurons have distinct functions depending on their location in the highly stratified retina and it is not known whether they are differentially affected by aging. Increasing knowledge of whether and how aging differentially alters these strata may help clinicians titrate the effects of disease from healthy aging.

This study had two objectives. First, we wanted to characterize the magnitude and spatial pattern of age-related loss in retinal layers within the macula in a multi-centre study of a large number of healthy subjects. Second, we wanted to contrast these aging effects in the macula to those in the neuroretinal rim and RNFL to determine whether they were different among structures that are commonly evaluated for the diagnosis and follow-up of glaucoma.

METHODS

Participants

We included subjects who self-identified as being White Caucasian in 5 centres (one in Canada and two each in the United States and Germany). Subjects were recruited by advertisement in local media, bulletin boards and from a registry of subjects who had previously taken part in other studies. Approximately equal numbers of subjects were recruited in each decade group from 20-90 years. The Ethics Review Board of each institution approved the study, and in accordance with the Declaration of Helsinki, all subjects gave informed consent to participate.

A verbal screening for participation was first conducted. A medical history was then obtained, followed by an ocular health assessment that included visual acuity measurement with the standard Snellen or Early Treatment Diabetic Retinopathy Study (ETDRS) chart, refraction, keratometry and axial length measurement. Visual field examination was then conducted with standard automated perimetry (Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) and the 24-2 Swedish Interactive Thresholding Algorithm), repeated once if not deemed reliable or within normal limits (see below), OCT examination (see below), ophthalmoscopic examination of the posterior pole and ONH stereophotography. Finally, Goldmann applanation tonometry and pachymetry were performed.

Subjects were included into the study if all the following inclusion criteria were met: (1) age between 20 and 90 years; (2) clinically normal eye examination without clinically significant vitreo-retinal or choroidal disease and prior intraocular surgery except cataract or refractive surgery; (3) intraocular pressure ≤ 21 mm Hg; (4) best corrected visual acuity $\geq 20/40$; (5) refractive error within 6 D spherical error and 2 D astigmatic error; and (6) normal visual field with the Glaucoma Hemifield Test and Mean Deviation within normal limits. Subjects were excluded if any of the following were found: (1) unreliable visual field examination based on the reliability indices and the perimetrist's notes; (2) ONH photographs of insufficient quality; (3) OCT images of insufficient quality (see below).

If eligible, all test procedures were carried out in both eyes of each subject. However, for the purpose of this study, data analysis was performed in one randomly selected eye only.

Optical coherence tomography

The ONH, peripapillary retina and macula were scanned with acquisition software that considered each subject's own fovea to Bruch's membrane opening (BMO) axis as horizontal (Spectralis, Heidey software version 5.4c, Heidelberg Engineering GmbH, Heidelberg, Germany).¹¹ The ONH was imaged with a pattern centred on BMO comprising 24 radially equidistant (15° apart) B-scans, each with 768 A-scans and averaged 25 times. The RNFL was imaged with a 12° circular scan, also centred on BMO, with 1,536 A-scans, averaged 100 times. Finally, the macula was imaged with a horizontal raster pattern, centred on the fovea, subtending $30^\circ \times 25^\circ$ and comprising 61 B-scans which were averaged 10 times. Corneal curvature measurements were entered into the instrument software to ensure accurate scaling of the measurements. All B-scans were manually examined for image

quality and poor quality scans, typically when structures were truncated, were removed. Additionally, only scans with an image quality score >20 were included.

The OCT B-scans were segmented with the device software. For the 24 ONH radial scans, BMO and the internal limiting membrane were first automatically segmented, and manually checked and corrected when necessary. The MRW at each of the 48 measurement points was calculated as the minimum distance between BMO and internal limiting membrane. For the peripapillary retina scans, the internal limiting membrane and the posterior border of the RNFL was segmented with RNFL thickness being the distance between these two surfaces. Finally for the macular scans, all layers from the internal limiting membrane to the external border of the outer nuclear layer (ONL) were segmented to derive the RNFL, the ganglion cell layer (GCL), the inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) thickness values. Layer segmentation in each B-scan was manually checked by two trained observers and corrected when necessary.

Data Analysis

All data were converted to right eye format. The macular scans were statistically analyzed globally (mean values within the central 6 mm, centred on the fovea) and additionally shown descriptively as twelve 30° clock-hour sectors (except within the central 1 mm), according to the fovea to BMO axis. Each clock sector was divided into sub-sectors every 0.5 mm along the radius. Significance of differences in variables among groups was determined with analysis of variance. Strengths of associations were determined with the coefficient of determination (R^2), while rate estimates were determined with ordinary least squares regression. The confidence intervals of these rate estimates were derived by creating 1000 bootstrapped samples. The relationship between both the global and temporal (90° subtense centred on the FoBMO axis) sectoral MRW and RNFL, and macular GCL thickness was also determined with the Pearson correlation coefficients. Statistical differences between correlations was determined with the Williams' test for comparing two correlations in dependent groups with overlapping variables.¹² Statistical analyses were performed with SPSS Statistics (v. 25 for the Macintosh, IBM, Armonk, NY) and R (version 3.3.1., R Core Team, Vienna, Austria).

RESULTS

A total of 259 subjects were enrolled and underwent the study procedures. Of these, 13 (5.0%) were excluded because the OCT images did not meet the image quality criteria. The median age of the remaining 246 subjects was 52.9 years, with a range of 19.8 to 87.3 years. There were no differences among the decade groups in sex distribution, IOP or BMO area ($P > 0.24$). There was, however, a statistically significant difference in axial length among the age groups, ranging from a mean of 23.45 mm in those aged from 40-50 years to a mean of 24.11 mm in those aged less than 30 years ($P = 0.02$). There were no significant differences in age, sex distribution, IOP, or BMO area among the 5 centres ($P > 0.21$).

The mean thickness maps for the 6 macular layers are shown in Figure 1. The central 1 mm of the macula was relatively thin compared to the surrounding sectors for all layers except the ONL, which was thicker, corresponding to the higher density of photoreceptors in the

fovea. Outside of the central 1 mm, all layers became progressively thinner with eccentricity, except the RNFL, which was thicker nasally compared to temporally (Fig. 1). There was no statistically significant correlation between axial length and any of the macular parameters except ONL thickness ($r = -0.16$, $P = 0.01$), however, this correlation was practically weak as age explained only 2% of the variation in ONL thickness. There were no differences in the thickness values of the 6 macular layers among the 5 centres ($P > 0.10$).

There was a significant decrease in the mean thickness of the macular GCL, IPL and INL with age ($P < 0.01$), however, the strength of the relationship was greatest for the GCL ($R^2 = 0.28$) and IPL ($R^2 = 0.22$, Fig. 2). The rate of change (95% CI) of GCL, IPL and INL thickness was -0.11 (-0.13 to -0.09), -0.07 (-0.08 to -0.05) and -0.03 (-0.04 to -0.01) $\mu\text{m}/\text{y}$, respectively, corresponding to 2.82 (2.29 to 3.32), 2.10 (1.61 to 2.57), and 0.78 (0.31 to 1.22)% loss per decade. There were no significant changes in the thickness of the macular RNFL, OPL and ONL with age (Fig. 2).

For the 3 layers with significant change in mean thickness with age (i.e., GCL, IPL and INL), the sectoral pattern of change indicated a faster rate of change in an annular pattern between 1 and 2 mm from the central 1 mm (Fig. 3). However, the same data expressed as a percentage change indicated a more spatially homogenous pattern (Fig. 4). While change in mean ONL thickness was not statistically significant, the spatial pattern showed a negative change in most sectors (Fig. 4). However, because of the relatively high value of ONL thickness, the percentage change with age was more modest. Changes in macular RNFL showed apparent increase in thickness in the nasal sectors and decreases in the temporal sectors (Figs. 3 and 4), however most of these changes were small compared to GCL and IPL changes. While most sectors showed a decrease in OPL thickness, there were sectors corresponding to the 1, 4 and 5 'o clock sectors that demonstrated an increase in OPL thickness with age (Fig. 3 and 4).

Of these 246 subjects, all had acceptable quality ONH scans, whereas 218 (89%) had acceptable peripapillary RNFL scans. There was a significant age-related decline (CI) in the global MRW (-1.22 [-1.68 to -0.87] $\mu\text{m}/\text{y}$; equivalent to 3.75 (2.62 to 4.99)% loss per decade, Fig. 5, available online) and peripapillary RNFL thickness (-0.20 [-0.26 to -0.14] $\mu\text{m}/\text{y}$; equivalent to 2.03 [1.40 to 2.67]% loss per decade, Fig. 5, available online). However, this association with age ($R^2 = 0.14$, $P < 0.01$; for both) was statistically weaker than for macular GCL ($P < 0.02$) but not IPL ($P > 0.21$) thickness.

The macular GCL thickness was significantly more correlated with global peripapillary RNFL thickness compared to MRW ($r = 0.63$ and 0.40 respectively, $P < 0.01$; Fig. 6). On the other hand, the correlation between macular GCL thickness and the temporal peripapillary RNFL thickness and temporal MRW was weaker compared to the respective global values, and not significantly different ($r = 0.27$ and 0.34 respectively, $P = 0.51$; Fig. 6).

DISCUSSION

The results of this study confirm previous histological^{13–15} and OCT^{16,14} evidence that the central foveal RNFL GCL, IPL, INL and OPL thickness is less compared to adjacent

macular areas, corresponding to the displacement of these layers to form the foveal pit. In contrast, the ONL is substantially thicker, corresponding to the high density of photoreceptors in the foveal avascular zone.

The recent emphasis on macular visual field testing and imaging in glaucoma diagnostics is logical since the density of retinal ganglion cells (RGCs), the primary class of retinal neuron lost in glaucoma, is highest in the macula. Approximately 7% of all RGCs are contained within the central 2 mm, while 26% and 39% are contained within the central 4 mm and 6 mm, respectively.¹⁷ Most OCT devices do not distinguish between the macular GCL and IPL, and with or without the RNFL, have termed these layers as the ganglion cell complex. Nonetheless, evidence indicates that the ganglion cell complex has equivalent diagnostic sensitivity for glaucoma when compared to conventional parameters such as neuroretinal rim width or peripapillary RNFL thickness.^{18–22} Most studies in the field also show that macular parameters identify a subset of patients not identified as being abnormal by rim or RNFL parameters.^{23–25}

Our results demonstrate that loss of the GCL occurs at around 3% per decade, a comparable magnitude of RGC loss determined in histopathological studies, which generally report a rate of loss of 0.8 to 4.5% per decade.^{26–28} A slightly lower percentage loss was observed in the IPL. In addition to RGC soma, the GCL also contains displaced amacrine cells¹⁷ and other cell types, including astrocytes and microglia,¹⁷ the latter being especially relevant after RGC loss.²⁹ Similarly, in addition to RGC axons, the RNFL has a substantial glial content that in some locations can exceed 40%,³⁰ as well as a vascular content that constitutes around 15%.³¹ The remodeling that occurs as a result of RGC loss and aging may mask neuronal loss. Indeed, in eyes with optic nerve trauma resulting in no light perception, the peripapillary RNFL thickness does not reduce to zero, underlining the significance of non-axonal components in RNFL.³² On the other hand, changes in the neuroretinal rim due to glaucoma can occur prior to neuronal loss suggesting that conformational changes in the optic nerve influence MRW measurements.^{33, 34} Taken together, these findings indicate that OCT measured changes do not necessarily equal somal or axonal loss.

We showed a significantly stronger relationship between the macular GCL and global peripapillary RNFL thickness compared to global MRW. This finding implies that the axonal component of the peripapillary RNFL more closely relates to the somal component of the GCL, and that the magnitude of the non-axonal component of the rim is larger and possibly more variable among individuals. These relationships could also suggest that the nature of remodeling that occurs with age is more significant in the rim than in the RNFL, or that its extent is more variable in the rim compared to the GCL and RNFL. Therefore, it is reasonable to propose that the measurements of the macular GCL and peripapillary RNFL more accurately reflect axonal loss. Indeed, evidence from normal and glaucomatous non-human primates in whom axonal counts were obtained histologically immediately following OCT imaging indicated that the peripapillary RNFL was a more accurate indicator of axonal counts than MRW.³⁵

The 90° temporal sector of the peripapillary rim and RNFL, constituting the papillo-macular bundle, corresponds to the majority of macular RGCs. The superior and inferior temporal rim and peripapillary RNFL sectors correspond additionally to RGCs in the temporal macula.³⁶ Nonetheless, it would still be expected that the correlation between macular GCL thickness, and MRW and RNFL thickness in the temporal sector would be higher compared to their global counterparts. However, our findings indicated otherwise. The reasons for these paradoxical findings are unclear, however, it is possible that the temporal rim and RNFL contain a higher proportion of non-axonal components. In non-human primates, Fortune and colleagues³⁷ found that there was a concomitant decrease in blood vessel diameter and RNFL thickness with age which possibly overestimates the magnitude of age-related axonal loss as blood vessels are invariably included in RNFL thickness measurements. Since the temporal sector does not contain large blood vessels, the relative impact of aging on MRW and RNFL thickness would be less compared to other sectors and lead to a weaker correlation with macular GCL thickness.

There is a paucity of published studies of OCT-measured thickness changes with age in the individual retinal layers. Nieves-Moreno and colleagues³⁸ reported statistically significant thinning of the GCL and IPL at $-0.05 \mu\text{m}/\text{y}$ each; figures that are not dissimilar to those in this study ($-0.11 \mu\text{m}/\text{y}$ and $-0.07 \mu\text{m}/\text{y}$, respectively). However, the R^2 values calculated in their study, and those of Demirkaya and colleagues,³⁹ are considerably lower compared to those in the present study (0.03 and 0.07, respectively compared to 28 for the GCL, and 0.11 and 0.07, respectively compared to 0.22 for the IPL). The reasons for these differences are not obvious given that the age range of the subjects and the mean values of the individual layers are similar in all three studies. However, it is notable that unlike the current study, neither Nieves-Moreno and colleagues³⁸ or Demirkaya and colleagues³⁹ appeared to have corroborated the automated layer segmentations.

Unlike the global peripapillary RNFL,⁴⁰ the macular RNFL did not show a thickness change with age. The average macular RNFL thickness was approximately one-third of that of the peripapillary RNFL, and therefore it is possible that the aging effect may have been correspondingly too small to detect. However, unlike all other macular layers, the macular RNFL is less symmetric, with greater thickness nasally compared to temporally. The nasal macular RNFL sectors demonstrated an increase in thickness with age, in contrast to the distal temporal RNFL, which showed a decrease. These observations are compatible with our previous finding of a negligible aging effect in the temporal peripapillary RNFL, but a significant decrease in the inferior and superior temporal peripapillary RNFL thickness.⁴⁰ Another possible reason for the lack of age-related change in the macular RNFL thickness could be that the degree of somal loss in the macular GCL is overestimated, perhaps due to shrinkage of RGCs that does not result in RNFL dropout in the macular RNFL.

The largest and most statistically significant changes in the macular layers with age occurred in the GCL and IPL, explaining around 28% and 22% of the variation in those layers respectively. The association of age with the GCL was twice as high as that for MRW or peripapillary RNFL thickness. Much research has highlighted the importance of aging as a significant factor in the development^{41, 42} and progression of glaucoma.^{43, 44} Indeed, clinical and histopathological evidence supports a convergence between the effects exerted by

glaucoma and aging.⁷ Because the macular GCL exhibits a more significant hallmark of aging compared to other neuroretinal parameters (in spite of the comparable percentage loss), an emphasis on macular imaging could enhance the detection of glaucoma and accurately monitor its rate of progression. Certainly, there is emerging evidence from macular imaging and perimetry studies to support this approach.⁴⁵ Ultimately, the utility of the GCL and IPL for tracking glaucoma progression compared to other neuroretinal parameters also depends on their relative magnitudes change with disease. If the relationship between the inner macular parameters and aging were weak (producing a large spread in values) then the ability to discern changes due to glaucoma may render the parameters less effective. On the other hand, if the relationship were statistically stronger, the changes due to glaucoma could be lesser in magnitude, but more readily detectable.

There was weaker evidence indicating loss of the INL with age. While statistically significant, there was less than 1% loss in INL thickness per decade. There is little supporting evidence in the literature as most studies have combined the outer retinal layers. A negative association between glaucoma severity and INL thickness has been reported,^{46, 47} suggesting possible microcystic formation⁴⁸ or activation of Müller cells in glaucoma.^{49, 50} We were not able to demonstrate a statistically significant change in ONL thickness with age. Histological evidence indicates loss of photoreceptors with age^{51, 52} in the order of 2-4% per decade,⁵² however, there is selective loss of rods in the central retina with a relative preservation of cones.⁵³ The space vacated by lost rods is filled in by larger rod inner segments and could be the reason why we were not able to demonstrate a statistically significant decrease of ONL thickness with age.⁵³

Our study assumes that cross-sectional data offer a valid surrogate for longitudinally derived observations on age-related changes. On the other hand, cross-sectional studies typically afford larger sample sizes and a wider age range in contrast to longitudinal studies, which have more limited sample sizes and follow-up periods that seldom exceed 10 years. All included data had to have high quality for inclusion and our sample did not contain subjects with high refractive error, hence results in unselected normal populations may be different. Our findings are limited to those in White subjects. Emerging evidence with OCT suggest that race-specific findings are likely to be significant.⁵⁴ There is active OCT research in many laboratories to study the interaction between age and race in glaucoma.

In summary, our study demonstrated a significant decrease in the macular GCL, IPL and INL with age. There was a significantly greater association with age in the macular parameters compared to that in the peripapillary RNFL and rim. Taken together, our results show that age-related structural changes are most accurately measured with macular OCT imaging.

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Age-related loss is twice as more effectively detected in the macular ganglion cell and inner plexiform layers compared to the neuroretinal rim and peripapillary retinal nerve fibre layer.

Figure 1.

Sectoral mean thickness of the macular retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) in right eye format. The innermost circle has a diameter of 1 mm while the outermost circle has a diameter of 6 mm, with the diameter of each concentric circle incremented by 1 mm (key, upper right). Each circle, except the centermost one, is divided into twelve 30° sectors. Layer thicknesses are in gray scale with the lightest sectors showing highest values and darkest sectors showing thinnest values (key, bottom right). Mean value of each layer is indicated. S, superior; T, temporal; I, inferior; N, nasal.

Figure 2.

Mean thickness change of the macular retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) with age. Coefficient of determination (R^2) and rate of loss shown for each layer. Line of best fit indicated for only those layers with a statistically significant change with age.

Figure 3.

Sectoral mean rate of the macular retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) thickness change with age in right eye format. The innermost circle has a diameter of 1 mm while the outermost circle has a diameter of 6 mm, with the diameter of each concentric circle incremented by 1 mm (key, upper right). Each circle, except the centermost one, is divided into twelve 30° sectors. Rates are in colour scale with the reddest sectors showing the most negative rates and greenest sectors showing the most positive rates (key, bottom right). Mean rate of change for each layer is indicated. S, superior; T, temporal; I, inferior; N, nasal.

Figure 4.

Sectoral mean rate of the macular retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) thickness change with age in right eye format expressed as a percentage. The innermost circle has a diameter of 1 mm while the outermost circle has a diameter of 6 mm, with the diameter of each concentric circle incremented by 1 mm (key, upper right). Each circle, except the centermost one, is divided into twelve 30° sectors. Rates are in colour scale with the reddest sectors showing the most negative rates and greenest sectors showing the most positive rates (key, bottom right). Mean percentage rate of change for each layer is indicated. S, superior; T, temporal; I, inferior; N, nasal.

Figure 5.

Relation between global minimum rim width (MRW) and peripapillary retinal nerve fibre layer (RNFL) thickness with age ($-1.34 \mu\text{m}/\text{y}$ and $-0.21 \mu\text{m}/\text{y}$, respectively). Lines of best fit indicated and coefficients of determination (R^2) are shown.

Figure 6.

Relation between macular ganglion cell layer (GCL) thickness and minimum rim width (MRW) and peripapillary retinal nerve fibre layer (RNFL) thickness globally (top) and in the temporal 90° sector (bottom). Pearson's correlation coefficients (r) are indicated.