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The limits of selection during maize domestication

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The domestication of all major crop plants occurred during a brief period in human history about 10,000 years ago[1]. During this time, ancient agriculturalists selected seed of preferred forms and culled out seed of undesirable types to produce each subsequent generation. Consequently, favoured alleles at genes controlling traits of interest increased in frequency, ultimately reaching fixation. When selection is strong, domestication has the potential to drastically reduce genetic diversity in a crop. To understand the impact of selection during maize domestication, we examined nucleotide polymorphism in *teosinte branched1*, a gene involved in maize evolution[2]. Here we show that the effects of selection were limited to the gene's regulatory region and cannot be detected in the protein-coding region. Although selection was apparently strong, high rates of recombination and a prolonged domestication period probably limited its effects. Our results help to explain why maize is such a variable crop. They also suggest that maize domestication required hundreds of years, and confirm previous evidence that maize was domesticated from Balsas teosinte of southwestern Mexico.

Several lines of evidence indicate that maize is a domesticated form of the wild Mexican grass teosinte (*Zea mays* ssp. *parviglumis* or spp. *mexicana*)[3–5]. Archaeological evidence places the time of maize domestication between 5,000 and 10,000 BP[6]. Despite the recent derivation of maize from teosinte, these plants differ profoundly in morphology[5]. One major difference is that teosinte typically has long branches with tassels at their tips whereas maize possesses short branches tipped by ears. Genetic analyses have identified *teosinte branched1* (*tb1*) as the gene that largely controls this difference[2]. Recent cloning of *tb1* (ref. 7) provides the first opportunity to examine the effects of selection on a 'domestication gene' and to infer from these effects the nature of the domestication process.

During development, *tb1* acts as a repressor of organ growth in those organs in which its messenger RNA accumulates. Consistent with this interpretation, plants carrying the maize allele accumulate more *tb1* mRNA in lateral-branch primordia and have shorter branches (that is, greater repression of branch elongation) than plants carrying the teosinte allele, which accumulate less *tb1* mRNA and have longer branches[7]. This difference in message accumulation between the maize and teosinte alleles suggests that the evolutionary switch from teosinte to maize involved changes in the regulatory regions of *tb1*.

Domestication should strongly reduce sequence diversity at genes controlling traits of human interest. To test this expectation for *tb1*, we sampled a 2.9-kilobase (kb) region (Fig. 1) including most of the predicted transcriptional unit (TU) and 1.1 kb of the 5′ non-transcribed region (NTR) from a diverse sample of maize and teosinte (Table 1). Two measures of genetic diversity were calculated: π, the expected heterozygosity per nucleotide site, and $\hat{\theta}$, an estimate of $4N_e\mu$, where N_e is the effective population size and μ the mutation rate per nucleotide[8]. Within the TU, maize possesses 39% of the diversity found in teosinte, which is not significantly lower than that (71%) seen for the neutral gene, *Adh1* (Table 2). However, within the NTR, maize possesses only 3% of the diversity found in teosinte. Thus, selection during domestication is associated with strongly reduced diversity in the NTR where regulatory sequences are typically found, but more modestly reduced diversity in the TU.

If *tb1* contributed to the morphological evolution of maize, then in the *tb1* phylogeny for maize and teosinte, maize sequences should form a single clade with only minor differentiation among them. Moreover, the type of teosinte most closely related to the direct ancestor of maize should be associated with the maize clade. In contrast, previous research with neutral genes not involved in maize evolution has shown that maize sequences for such genes are dispersed among multiple clades owing to the effects of lineage sorting[9–13]. A phylogeny for the *tb1* TU fits the expectation of a neutral gene, with maize sequences falling into multiple clades (Fig. 2a). However, the phylogeny for the NTR shows all maize on a single, well-supported clade (I) (Fig. 2b), as predicted for a gene involved in maize evolution. There are five teosinte sequences

Table 1 List of taxa and collections sampled

Taxon	Sample	Collection	Origin
MAIZE	**1L**, 1P	BOV396	Bolivia
	2L, 2P	ECU969	Ecuador
	3L, 3P	GUA131	Guatemala
	4L	JAL78	Mexico
	5P	JAL44	Mexico
	6L	MEX7	Mexico
	7L	MOR17	Mexico
	8L	PI213778	North Dakota
	9L	PI218177	Arizona
	10L	SIN2	Mexico
	11L	YUC7B	Mexico
	12L, 12P	VEN604	Venezuela
	13L	W22	Wisconsin
PAR	**14L**, **15L**	BK2	Chilpancingo, Guerrero
	16L, **17L**	BK4	Palo Blanco, Guerrero
	18L	K71-4	Palo Blanco, Guerrero
	19L-A, **B**	B4	Teloloapan, Guerrero
	20P	BK6	Valle de Bravo, Mexico
	21P	IN1480	Jirosto, Jalisco
	22P	IC308	Tzitzio, Michoacan
	23P	BK1	Mazatlan, Guerrero
	24P	Z967	El Rodeo, Jalisco
MEX	**25L**	I28620	Texcoco, Mexico
	26L-A, **B**	B2438	Nobogame, Chihuahua
	27P	D625	Durango, Durango
	28P	D642	Tlamanalco, Mexico
	29P	D479	Texcoco, Mexico
	30P	P11066	Degollado, Jalisco
	31P	W45461	Panindicuaro, Michoacan
	32P	J110	Toluca, Mexico
DIP	**33L**	G1120	Las Joyas, Jalisco

Taxa include *Zea mays* ssp. *mays* (MAIZE), ssp. *parviglumis* (PAR) and ssp. *mexicana* (MEX) and *Zea diploperennis* (DIP). Sequences isolated by λ cloning (L) and PCR (P). Samples for which we isolated and sequenced the 3′ end of the gene are shown in bold. Source of the teosinte collections include G. Beadle (B), B. Benz (Z), T. Cochrane (C), J. Doebley (D), R. Guzman (G), H. Iltis (I), T. A. Kato (K), J. Kermicle (J), M. Nee (N), L. Puga (P) and H. G. Wilkes (W).

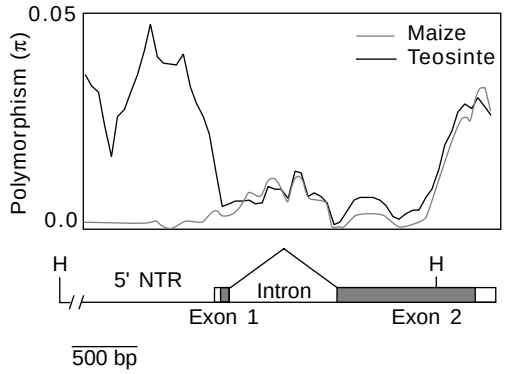

Figure 1 Predicted structure of *teosinte branched1* (ref. 25) and sliding-window analysis of polymorphism (π) in maize and teosinte. For the sliding-window analysis, π was calculated for segments of 300 bp at 50-bp intervals. Sequences used in the analysis were the subset of the λ-cloned sequences for which we isolated the 3′ end by PCR (Table 1). The position of the *Hin*dIII (H) restriction endonuclease sites used in λ cloning are shown, as are the predicted exons (rectangles) and coding region (stippled).

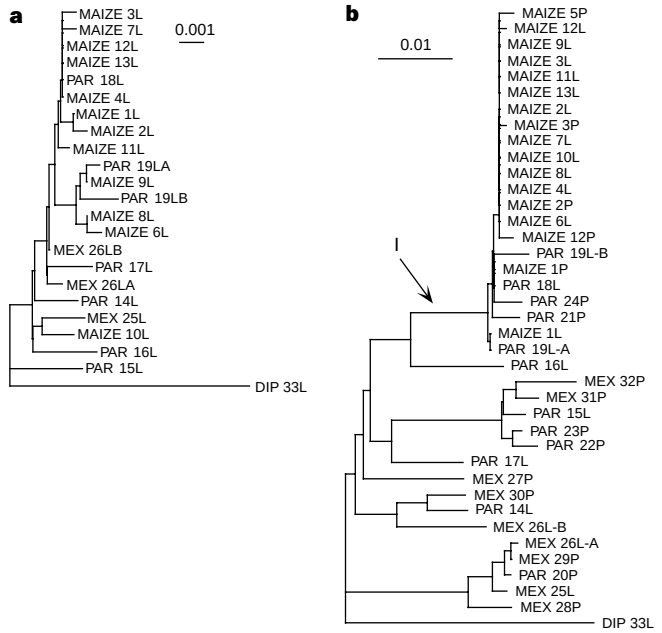

Figure 2 Neighbour-joining trees for *tb1* based on the 1,729-bp transcribed region (**a**) and the 1,143-bp 5′ non-transcribed region (**b**). Taxa include maize, ssp. *parviglumis* (PAR), ssp. *mexicana* (MEX) and the outgroup *Z. diploperennis* (DIP). Sample numbers follow the taxon names. Scale bars indicate the number of substitutions per site using Kimura's 2-parameter distances. Clade I was supported in 200 of 200 bootstrap resamplings of the original data. An initial analysis of the 5′ non-transcribed region using the 22 maize and teosinte λ-cloned sequences indicated that all maize alleles were derived from ssp. *parviglumis*. To confirm whether this result would be sustained with a larger sample, we isolated 16 additional sequences for a more comprehensive analysis (see Methods).

tightly associated with the maize sequences and all belong to ssp. *parviglumis*. The teosinte (sample 16L) basal to clade I also belongs to ssp. *parviglumis*. This phylogeny and previous research[14] provide compelling evidence that ssp. *parviglumis* (Balsas teosinte) is the progenitor of maize and suggest that maize arose in the Balsas river valley of southwestern Mexico, where this subspecies is native.

Although the phylogenies and the relative amount of nucleotide variation in maize suggest that selection has acted on *tb1*, we collected data on nucleotide polymorphism specifically to determine whether *tb1* has experienced a recent selective sweep. This determination was made using the HKA test[15], in which the ratio of polymorphism within a species (maize) to divergence from an outgroup (*Z. diploperennis*) for *tb1* was compared with this ratio for neutral genes. A recent selective sweep in maize would be expected to reduce this ratio for *tb1* relative to neutral genes. The HKA test was not significant for the TU, indicating that there is no evidence for selection on the coding region (Table 3). However, the test was highly significant for the NTR, indicating that selection has strongly reduced variation here. Remarkably, the HKA test for the NTR was significant even if the TU was used as the control. This shows that the 'hitchhiking' effect was so small that it did not even affect the entire gene.

The relative impact of selection on the NTR and TU can be readily seen in a plot of polymorphism (π) for maize and teosinte along the length of *tb1* (Fig. 1). Throughout the NTR, π is substantially lower in maize than in teosinte, reflecting the impact of selection. At the boundary between the NTR and the TU, π for teosinte drops precipitously, as expected, because there is greater constraint on coding regions; however, π for maize rises until it is nearly equal to π for teosinte. Finally, approaching the stop codon at the 3′ end of the gene, π rises steeply in both maize and teosinte, reflecting reduced constraint in this non-translated region. Figure 1 shows graphically how the impact of selection on polymorphism was narrowly focused on the NTR.

As further evidence that regulatory changes in the NTR rather than changes in protein function were involved in maize evolution, we examined the predicted amino-acid sequence of our maize and teosinte sequences. Because our maize and teosinte λ clones did not include the 3′ end of the TU unit, we isolated and sequenced an additional segment spanning the end of the λ clones to ~170 base pairs (bp) downstream of the stop codon (Table 1). Over the entire coding region, there are no fixed differences in the predicted amino-acid sequences between maize and teosinte.

Our analysis of nucleotide polymorphism in *tb1* provides compelling evidence that selection during maize domestication was aimed at the NTR, where regulatory elements are typically found. We had previously observed that the *tb1* mRNA for the maize allele accumulates at twice the level of that for the teosinte allele and proposed that changes in *tb1* regulation underlie maize evolution[7]. Combined evidence from polymorphism analysis and previous work on *tb1* mRNA levels are thus congruent, providing strong evidence that the short, ear-tipped lateral branches of maize evolved from the long, tassel-tipped branches of teosinte by human selection for novel regulatory elements in the NTR.

Although our data implicate selection on regulatory sequences during maize evolution, we found no fixed differences between

Table 2 Nucleotide polymorphism ($\pi/\hat{\theta}$) per bp (×1,000) in maize

Locus	MAIZE	MEX + PAR	PAR
tb1:NTR	0.47/0.93	33.08/35.52	28.68/32.57
tb1:TU	1.74/2.43	3.90/6.09	4.62/6.26
Adh1 (ref. 9)	15.72/14.13	–	17.38/20.01

Taxa include *Zea mays* ssp. *mays* (MAIZE), ssp. *parviglumis* (PAR) and ssp. *mexicana* (MEX). These values are based on the 12 maize and 10 teosinte sequences that were cloned in λ (see Table 1).

Table 3 HKA test of neutrality at *tb1* in maize

Test locus	*tb1* NTR	*tb1* TU	*tb1* NTR	*adh1* (ref. 9)	*adh2* (ref. 11)
Control loci	*adh1*, *adh2*	*adh1*, *adh2*	*tb1* TU		
Polymorphism	0.93	2.43	0.93	14.13	25.8
Divergence	52.55	12.73	52.55	21.25	23.6
Ratio	0.018	0.19	0.018	0.66	1.09
χ^2	13.58	2.70	8.24		
P	0.001	0.26	0.004		

Polymorphism ($\hat{\theta}$) and divergence (average pairwise differences between maize and *Z. diploperennis*) are reported per base pair (×1,000).

maize and teosinte within the 1.1 kb of NTR that we analysed. In fact, some maize and teosinte sequences (for example, maize 1P and *parviglumis* 18L) are nearly identical within this region, differing by only 1 bp in the length of a poly(A) track. This may indicate either that the selected site lies further upstream or that the differences between maize and teosinte are complex and depend on a group of polymorphisms rather than a single site[16]. Recombination between an upstream selected site and the region we sequenced could explain why maize is not fully separated from teosinte in the phylogeny (Fig. 2b).

Selection intensities during domestication are expected to be high because crop evolution involves dramatic changes in morphology within a short time. Under directional selection, the selection coefficient (s) is measured as the difference in relative fitness of the most fit and least fit genotypes, where fitness is the contribution of a genotype to the next generation. For example, $s = 0.01$ would indicate that 100 maize alleles would be passed to the next generation for every 99 teosinte alleles. A rough estimate of s requires a knowledge of the recombination rate (c, crossovers per bp per generation) and the distance (d) in bp from the selected site over which there has been a substantial reduction in nucleotide variation[17]:

$$d = 0.01s/c$$

For maize, recombination rates have been empirically measured for several genes, giving a mean value for c of $\sim 4 \times 10^{-7}$ (refs 18–21). Two observations allow a preliminary estimate of d: first, the substantial reduction in nucleotide variation is restricted to the NTR or promoter and does not extend into the TU, and, second, plant promoters are normally 2 kb or less in size (see Methods). Thus, the selected site is likely to be less than 2 kb from the TU and must be at least 1.1 kb from the TU since it does not appear to lie in the 1.1 kb of NTR that we sequenced. Using these values, s is estimated to be between 0.04 and 0.08. This estimate can be refined in the future by obtaining direct estimates of c in *tb1* and identifying the precise position of the selected site.

When s is known, one can estimate the time (T_f) required to bring the maize allele to fixation[22]. We assume that the initial frequency of the maize allele was $1/2N$, where N is the population size, and that gene action was additive[2]. We considered two population sizes during the time of selection: 1,000, which assumes teosinte was grown like a horticultural crop in gardens, and 100,000, which assumes it was grown like an agriculture crop but still over a limited geographical area. We assume values for s of 0.04 and 0.08 (see above). For these values, T_f ranges from 315 to 1,023 years. Thus, the morphological evolution of maize as controlled by *tb1* could have been rapid, over just several hundred years.

We were surprised that maize remained polymorphic for *tb1*, even within the NTR. To assess whether the observed level of variation at *tb1* in maize is consistent with previous estimates of mutation and recombination rates, population sizes and the time of maize domestication, we carried out coalescent simulations[23]. The simulations included a selective sweep modelled on a range of estimates for T_s (time since the selective sweep) and s (Table 4). To measure the effect of a selective sweep so that it reflects the present context of not knowing the actual site of selection, we measured the longest segment with zero, one or two polymorphic sites. The simulated mean values of these lengths are remarkably close to the observed data. Thus, even for genes under strong selection, domestication need not remove all variation. The ability of maize to remain polymorphic at *tb1* probably reflects high recombination rates over the hundreds of years required to bring the maize allele to fixation such that there was substantial recombination between the allele that initially harboured the selected site and other alleles in the population. By this means, considerable polymorphism was maintained in the coding region in the face of strong selection on the NTR.

Population-genetic analysis of domestication genes can provide a new view of the processes that sculpted the formation of crop species. For *tb1*, such analysis indicates that ancient agriculturalists exerted a strong selective force on *tb1* that has drastically reduced polymorphism in its regulatory region but not in its coding region. This observation is consistent with previous evidence that alterations in the regulation of *tb1* brought about the change from teosinte to maize plant architecture. We also infer that it took at least several hundred years to bring the maize allele of *tb1* to fixation. Finally, these analyses indicate that Balsas teosinte is the ancestor of maize, since all maize alleles sampled show a close and statistically robust phylogenetic association with this teosinte. □

Table 4 Results from coalescent simulations of the effect of the selective sweep during maize domestication on polymorphism in *tb1*

		Mean lengths (bp)			
T_s	s	0 PS	1 PS	2 PS	
5,000	0.04	682.80	796.20	875.60	Pred.
10,000	0.04	566.00	725.80	830.40	Pred.
5,000	0.08	1,068.40	1,233.20	1,329.00	Pred.
10,000	0.08	892.00	1,133.00	1,321.00	Pred.
–	–	440	760	1,035	Obs.

T_s is the time in generations since the end of the selective sweep, and s is the selection coefficient. The predicted (Pred.) and observed (Obs.) mean lengths of segments with zero, one and two polymorphic sites (PS) are shown.

Methods

Gene isolation. All sequences for population-genetic analysis were cloned into λ-ZAP (Stratagene) as *Hin*dIII fragments (Fig. 1). Isolation of the 3′ end of the gene for the sliding-window analysis (Fig. 1) and determination of the complete amino-acid sequence were accomplished by the PCR reaction (primers: TAGTTCATCGTCACACAGCC and CAATAACGCACACC AGGTCC). PCR was performed using PCR Supermix (Life Technologies) with one step of 4 min at 95 °C followed by 30 cycles of 1 min at 95 °C, 1 min at 60 °C and 3 min at 72 °C followed by 10 min at 72 °C. PCR products were cloned using the TOPO TA cloning kit (Invitrogen). Additional sequences of the NTR for phylogenetic analysis (Fig. 2) were isolated by PCR (primers: GCTATTGGCTACAAGTGACC and GGATAATGTGCACCAGGTGT). All sequences were deposited in GenBank (accession nos AF131649 to AF131705).

Statistics. Calculation of the range of reasonable values for s requires an estimate of the position of the selected site relative to the TU. The selected site is expected to lie within the NTR region in which regulatory sequences occur. Such regions typically extend 2 kb or less upstream of the TU in plants. For example, average gene density in *Arabidopsis* is one gene for every 4.8 kb[24]. With an average gene being about 2.5 kb long, this leaves about 2 kb for flanking regulatory sequences. Moreover, many reports in the literature reveal that 5′ regulatory sequences are usually within 1 kb of the transcription start site. For the coalescent simulations, the middle of the 4,000-bp sampled chromosomes was set as the point of a selective sweep. For the moderate values of s modelled, the use of deterministic allele frequency change will closely follow a stochastic selective sweep[17]. The population mutation rate (θ) was set to 0.0262 per bp, which is the estimated value from teosinte in the *tb1* NTR. The effective population size was set to the value (700,000) estimated for maize at *Adh1*, based on estimates of θ and μ for *Adh1* (ref. 9). The recombination rate (c) was set to 4×10^{-7} as described in the text. Sample size was 12, the same as the number of maize λ clones, and 200 runs were performed.

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Gaze direction controls response gain in primary visual-cortex neurons

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To localize objects in space, the brain needs to combine information about the position of the stimulus on the retinae with information about the location of the eyes in their orbits. Interaction between these two types of information occurs in several cortical areas[1–12], but the role of the primary visual cortex (area V1) in this process has remained unclear. Here we show that, for half the cells recorded in area V1 of behaving monkeys, the classically described visual responses are strongly modulated by gaze direction. Specifically, we find that selectivity for horizontal retinal disparity—the difference in the position of a stimulus on each retina which relates to relative object distance—and for stimulus orientation may be present at a given gaze direction, but be absent or poorly expressed at another direction. Shifts in preferred disparity also occurred in several neurons. These neural changes were most often present at the beginning of the visual response, suggesting a feedforward gain control by eye position signals. Cortical neural processes for encoding information about the three-dimensional position of a stimulus in space therefore start as early as area V1.

Area V1 is the first cortical area where orientation and horizontal retinal disparity are encoded[13–15]. Here, cells have oriented receptive fields that may occupy disparate locations on both retinae. Most of these cells have their activity (visual and/or spontaneous) modulated by the viewing distance in the straight-ahead sagittal direction[16,17]. But do such modulations also occur as a function of the direction of gaze? This would imply that V1 cells would be more dedicated to certain volumes of visual space, in which case changing the direction of gaze should affect some or all of the visual properties encoded in the primary visual cortex, such as horizontal retinal disparity and orientation selectivity.

We obtained data from 142 neurons in two monkeys that were trained to fixate a target at three different positions in the frontoparallel plane (Fig. 1a). For studies of both disparity and orientation, changes in gaze direction produced significant changes in neuronal activity in 54% ($n = 67$) of cells tested for disparity and 50% ($n = 104$) tested for orientation. The main effect was a significant change in the evoked firing rate (gain) in 72% of cells studied for disparity and in 85% studied for orientation. Shifts in preferred disparity angle were observed in 17% of cells; the remainder showed inconclusive changes in the tuning curves. Three examples of the gain effect on disparity coding are shown in Fig. 2. The cell shown in Fig. 2a is disparity selective with the preferred response in the plane of fixation (0°) when the monkey fixates in the centre of the screen or on the left, but shows a significant drop in the level of visual response, close to the spontaneous activity level, when the monkey fixates on the right. The cell shown in Fig. 2b exhibits significant progressive increase in the evoked firing rate in the plane of fixation (tuned 0°) from the left to the right direction of gaze. That shown in Fig. 2c displays a shift in preferred disparity angle: it has a preferred disparity angle in the plane of fixation (0°) for a gaze directed to the left, but shifts its peak just behind that plane (centred on 0.2°) for the right direction, with an intermediate step for the straight-ahead direction.

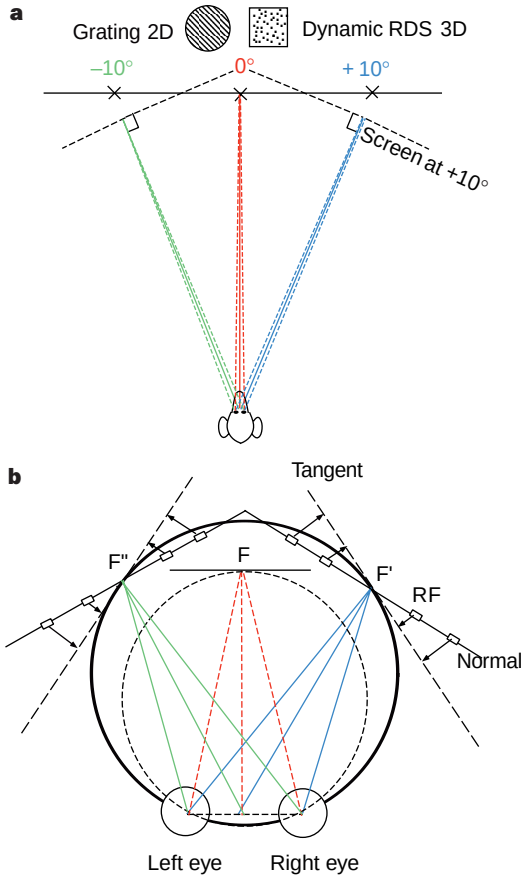

Figure 1 Experimental set-up. **a**, Dynamic random dot stereograms (RDS) and square-wave gratings were flashed on a video monitor screen subtending 42° or 32° of visual angle at three directions of gaze (straight ahead, 0°; left, –10°; and right, +10°) in the frontoparallel plane. For the left and right directions, the video monitor was rotated by 10° to maintain geometrical configurations with the viewing distance kept constant at 50 cm. Continuous lines of view represent the binocular axis. **b**, Vieth–Müller circles passing through both eyes and through fixation point for the three directions of gaze (F, F′ and F″) (adapted from ref. 19).