Behavioral/Cognitive

The Role of Visual Experience in Individual Differences of Brain Connectivity

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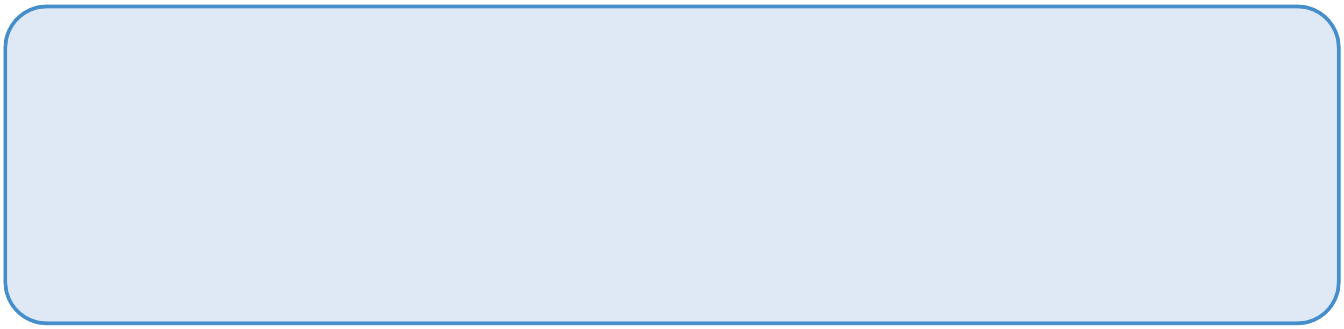
Visual cortex organization is highly consistent across individuals. But to what degree does this consistency depend on life experience, in particular sensory experience? In this study, we asked whether visual cortex reorganization in congenital blindness results in connectivity patterns that are particularly variable across individuals, focusing on resting-state functional connectivity (RSFC) patterns from the primary visual cortex. We show that the absence of shared visual experience results in more variable RSFC patterns across blind individuals than sighted controls. Increased variability is specifically found in areas that show a group difference between the blind and sighted in their RSFC. These findings reveal a relationship between brain plasticity and individual variability; reorganization manifests variably across individuals. We further investigated the different patterns of reorganization in the blind, showing that the connectivity to frontal regions, proposed to have a role in the reorganization of the visual cortex of the blind toward higher cognitive roles, is highly variable. Further, we link some of the variability in visual-to-frontal connectivity to another environmental factor—duration of formal education. Together, these findings show a role of postnatal sensory and socioeconomic experience in imposing consistency on brain organization. By revealing the idiosyncratic nature of neural reorganization, these findings highlight the importance of considering individual differences in fit-



temporal trajectory at the individual level as changes accumulate

Table 1. Characteristics of blind participants

Participant	Cohort	Gender	Age	Cause of blindness	Light perception	Handedness	Age of blindness onset
1	A	F	29	Microphthalmia	None	Right	0
2	A	F	23	Microphthalmia, retinal detachment	None	Left	0
3	A	F	30	Retinopathy of prematurity	None	Right	0
4	A	M	37	Retinopathy of prematurity	None	Right	0
5	A	F	38	Enophthalmus	None	Left	0
6	A	M	54	Retinopathy of prematurity	None	Right	0
7	A	M	23	Microphthalmia	None	Right	0
8	A	F	34	Retinopathy of prematurity	None	Right	0
9	A	M	31	Retinopathy of prematurity	None	Right	0
10	A	F	35	Retinoblastoma	None	Right	0
11	A	F	34	Microphthalmia	None	Left	0
12	A	F	30	Leber congenital amaurosis	Faint	Ambidextrous	0
13	A	M	42	Retinopathy of prematurity	Faint	Right	0
14	B	M	36	Microphthalmia	None	Ambidextrous	0
15	B	M	22	Microphthalmia	None	Right	0
16	B	M	33	Microphthalmia; microcornea	None	Right	0
17	B	M	48	Glaucoma	None	Right	0
18	B	F	46	Glaucoma	None	Right	0
19	B	M	40	Leukoma	Faint	Right	0
20	B	F	50	Cataracts; eyeball dysplasia	Faint	Right	0
21	B	M	57	Eyeball dysplasia	None	Right	0
22	B	F	43	Glaucoma	None	Right	0
23	B	M	48	Microphthalmia; cataracts; leukoma	None	Right	0
24	B	M	63	Glaucoma; leukoma	None	Right	0
25	B	F	41	Optic nerve atrophy	Faint	Right	0

Cohort A was acquired in Israel and comprised 13 blind adults and 18 sighted controls (

0.2 mm gap; multiband factor = 2, TR = 2000 ms, TE = 30 ms, FA = 90°, matrix size = 112 × 112, FOV = 224 × 224 mm, voxel size = 2 × 2 × 2 mm. T1-weighted anatomic images were acquired using a 3D MPRAGE sequence (192 slices, 1 mm thickness, TR = 2530 ms, TE = 2.98 ms, inversion time = 1100 ms, FA = 7°, FOV = 256 × 224 mm, voxel size = 0.5 × 0.5 × 1 mm, interpolated; matrix size = 512 × 448). Data of cohort B were downsampled to a resolution of 3 mm isovoxels for joint analysis with data from cohort A.

fMRI preprocessing

Data analysis was performed using the BrainVoyager 20 software package (Brain Innovation) and custom scripts in MATLAB (MathWorks) following standard preprocessing procedures. The first two images of each scan were excluded because of non-steady-state magnetization. Preprocessing of functional scans included 3D motion correction, slice scan time correction, bandpass filtering (0.01–0.1 Hz), and regression of spurious signals from the ventricles and white matter regions (defined using the grow-region function in BrainVoyager on the individual level). Head motion did not exceed 2 mm along any given axis or include spike-like motion of >1 mm in any direction. There was no difference in head displacement between the groups and cohorts (2 × 2 ANOVA for group X cohort; group effect, $F_{(1,53)} = 0.39$, $p = 0.53$; cohort effect, $F_{(1,53)} = 1.02$, $p = 0.32$; interaction $F_{(1,53)} = 1.26$, $p = 0.27$). Data were normalized to standard Talairach space (Talairach and Tournoux, 1988). Analyses were replicated (Extended Data Fig. 1-1) using global signal regression as a preprocesing step, known to aid in overcoming motion-derived artifacts and link to behavior (Ciric et al., 2017; Li et al., 2019), but also to introduce additional artifacts (e.g., introduction of anticorrelation, distortion of group differences, and exacerbation of distance-dependent motion artifacts; Murphy et al., 2009; Anderson et al., 2011; Power et al., 2012; Saad et al., 2012; Satterthwaite et al., 2012; Gotts et al., 2013; Hahamy et al., 2014; Ciric et al., 2017). To overcome differences originating from the two datasets, scan parameters and cohorts, we applied *post hoc* standardization (*z* normalization of the data), shown to dramatically reduce site-related effects (Yan et al., 2013). An additional step to exclude site-related effects was the integration of the cohort grouping factor explicitly in the RSFC ANOVA (see below) and study effects related to group regardless of the cohort (as evident by the minimal cohort effects remaining in the analyzed data; see Fig. 2*B*).

Seed regions of interest

The region of interest (ROI) for the primary visual cortex (V1) was defined from an independent localizer, acquired in a separate group of 14 sighted subjects (Striem-Amit et al., 2015) using a standard phase-encoded retinotopic mapping protocol, with eccentricity and polar mapping of ring and wedge stimuli, respectively (Engel et al., 1994; Sereno et al., 1995; Wandell et al., 2007; Wandell and Winawer, 2011). The experimental detail can be found in Striem-Amit et al. (2015). Polar mapping data were used to define the borders of V1, used as a seed ROI for the RSFC analyses. Control seed ROIs included anatomically defined Brodmann areas (from the anatomic atlas in BrainVoyager) with the exception of visual association areas BA 18, 19, and 37. BAs 18 and 19 were tested separately (Extended Data Fig. 1-3).

RSFC variability analyses

Individual time courses from the V1 seed ROI were sampled from each of the participants, *z* transformed and used as individual predictors in a *z*-normalized GLM analysis, with individual motion estimates (six degrees of freedom and their first derivatives) as nuisance predictors. Individual RSFC maps were spatially smoothed with a 6 mm full-width-at-half-maximum Gaussian kernel for group analyses. Data were analyzed with a 2 × 2 random effects ANOVA (Group {blind, sighted} × Cohort {A,B}) at the voxel level. In addition to the main effect of Group (see Fig. 2*A*; Fig. 2*B*,*C*, showing limited cohort effect and group X cohort interaction), we calculated the Brown–Forsythe test for equal variance for this main effect, testing whether the two groups differed in their interindividual variability of the RSFC values (Fig. 1*A*). The Brown–Forsythe test (Brown and Forsythe, 1974) is a homogeneity of variance test similar to Levene's test, conventionally used to test for variability differences, but uses the median instead of the mean, safeguarding against false positives in cases of skewed data distribution (Olejnik and Algina, 1987). The same analyses were performed for all nonvisual control seed ROIs (Brodmann areas) for the comparison of variability and reorganization correlation (details below). The minimum significance level of all results presented in this study was set to $p < 0.05$, corrected for multiple

comparisons within the gray matter volume using the spatial extent method (a set-level statistical inference correction; Friston et al., 1994; Forman et al., 1995). Correction was based on the Monte Carlo simulation approach, extended to 3D datasets using the threshold size plug-in for BrainVoyager QX. We additionally computed the variability of RSFC within each group separately, using normalized data of each group to overcome possible effects of the different cohorts on the mean and SD of the RSFC. To inspect the direction of the variability group effect, we computed the ratio of variability between the groups ($\text{Variability}_{\text{Blind}}/\text{Variability}_{\text{Sighted}}$; Fig. 1*B*) for each voxel showing a significant Brown–Forsythe test effect ($p < 0.05$, corrected). The same calculation of the variability ratio was atS59(v)c.2(l)1.(io)1.91(e)-.16ocTbswutho

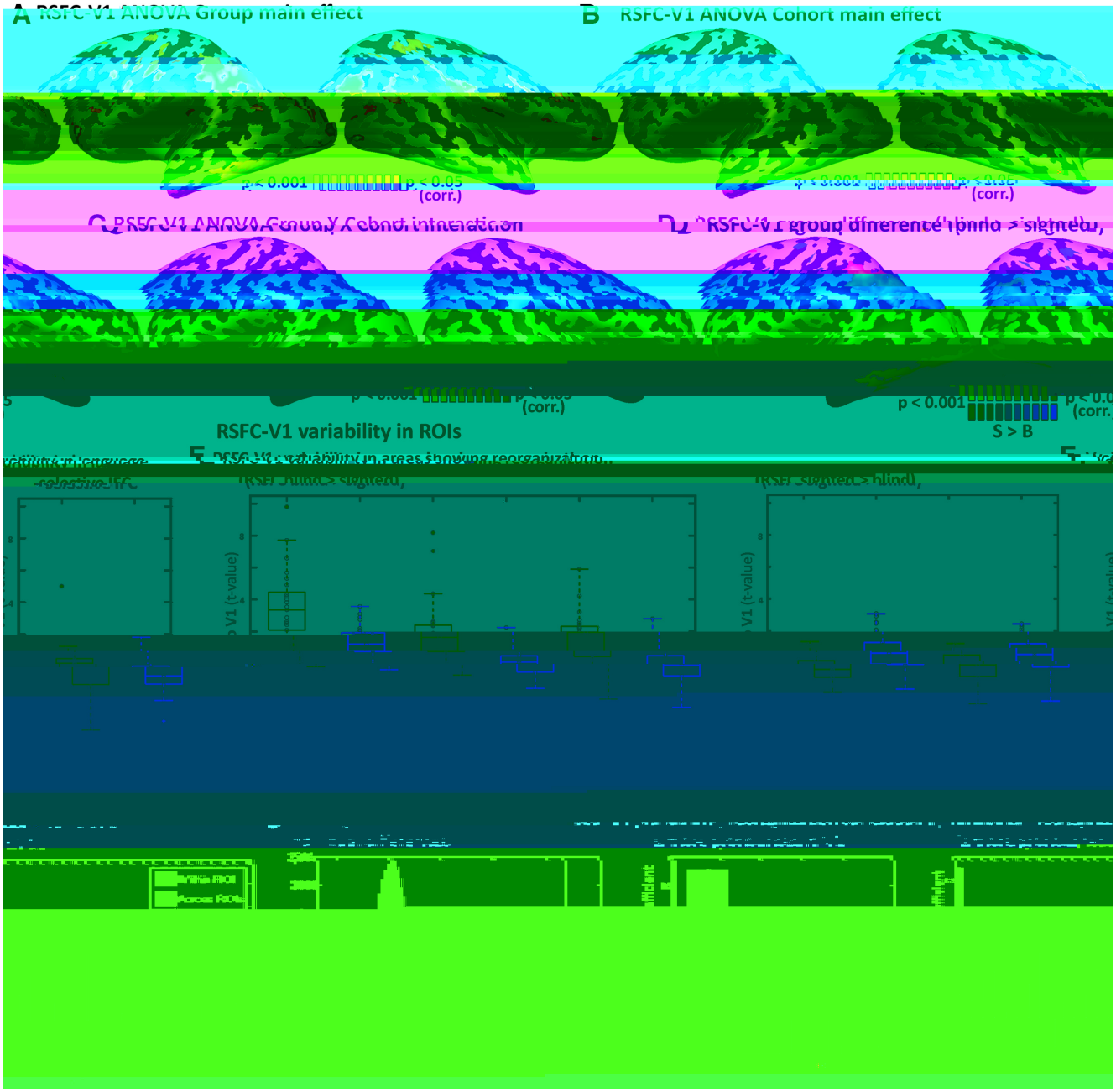


Figure 2. Brain reorganization in blindness is associated with increased interindividual variability. ***A-C***, Main effects and interactions for the Group X Cohort ANOVA for V1-RSFC. ***A***, The effect of sight across the cohorts is depicted. As reported before, the blind and sighted differed in their RSFC from the primary visual cortex to visual, parietal, and frontal regions. ***B***, The main effect of cohort across the groups, showing little difference focused in the right superior frontal cortex. ***C***, The Group X Cohort interaction shows no significant effect. ***D***, Increased V1-seeded RSFC in blindness is found in the visual streams, as well as in the bilateral IFC. ***E***, ***F***, The blind show increased variability in their V1-seeded RSFC to left ventral stream, dorsal stream, and IFC frontal areas. Box plots are presented for the blind and sighted in red and blue, respectively. The central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Error bars represent the standard deviation. Individual participant data are presented in circles. ***E***, Within the areas showing increased RSFC in the blind (Fig. 2*D*). The sensorimotor cortex, showing decreased V1-RSFC in blindness, showed similar but slightly lower variability in the blind. ***F***, The blind show increased variability in their V1-seeded RSFC to a language-selective IFC ROI, defined by preference toward words compared with pseudowords. ***G***, Overall across the brain, areas showing changes in RSFC in blindness also show increased variability across blind participants. The concordance correlation coefficient was calculated between the RSFC group difference and RSFC change in variability for the V1 seed (red line) and compared with a spatial permutation test (distribution in black). ***H***, The link between reorganization and increased variability in blindness is more pronounced in V1. Correlation between the two maps for the V1 seed was significantly greater than in correlating across seeds and significantly greater for V1 compared with other nonvisual Brodmann areas. Error bars represent the standard deviation. ***I***, The link between reorganization and increased variability in blindness is presented for V1 (bar, far left) and all control nonvisual Brodmann areas in blue. For each area, the across-seed correlation is shown in red. The within-seed correlation for all control areas was lower than for V1; however, the comparison between within- and across-seed correlation was significant, suggesting that more broadly, reorganization manifests in greater variability.

Clustering analysis

To qualitatively explore individual differences in the RSFC from the visual cortex of the blind, we performed a hierarchical clustering analysis across subjects' V1-seeded RSFC maps, using RSFC values for each individual from each of the Brodmann areas in the BrainVoyager atlas (see above). Distance was calculated as the correlation between individual RSFC vectors, implemented in MATLAB (MathWorks). A dendrogram of the distances across all participants was computed based on complete distance between clusters (Fig. 3*A*; Fig. 3*B* shows the underlying correlation dissimilarity matrix). As a preliminary quantitative exploration of

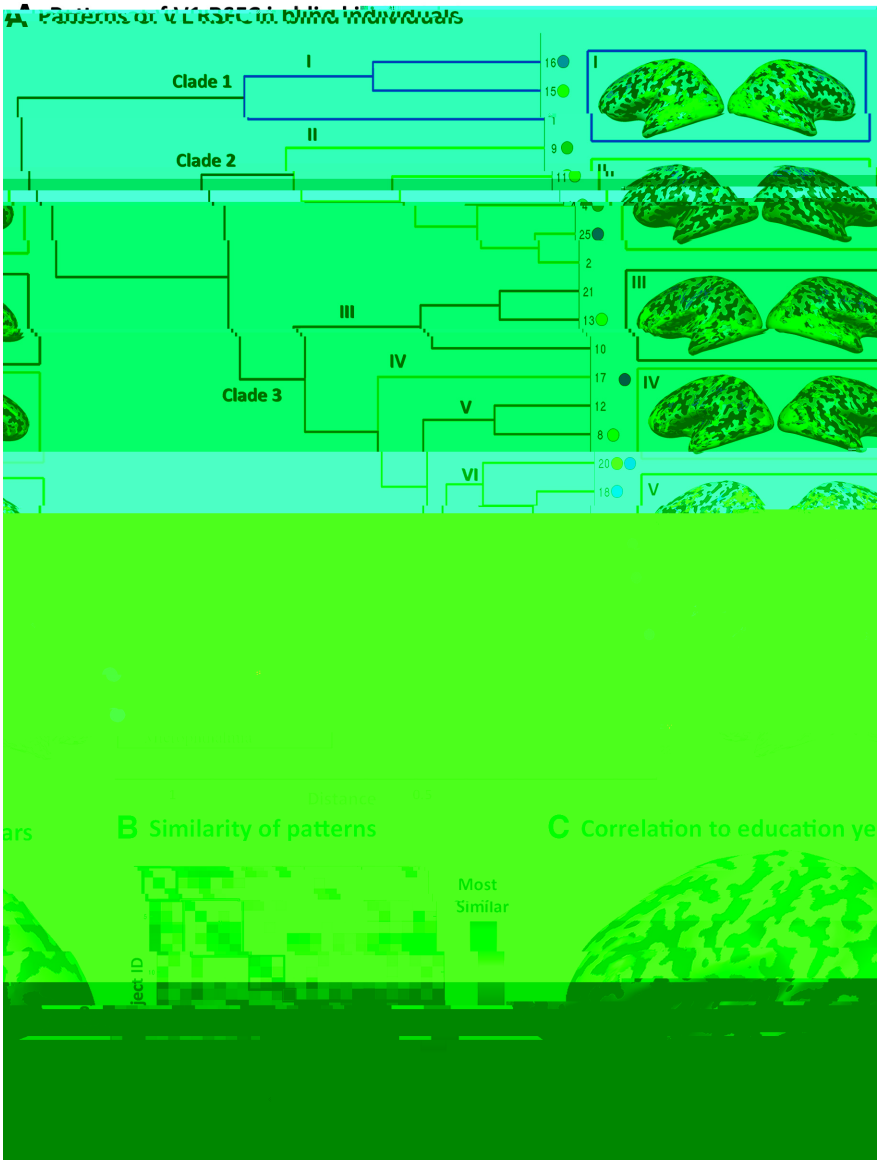


Figure 3. Patterns of brain reorganization in blindness. ***A***, V1-RSFC of each individual blind participant to each Brodmann area was used to compute hierarchical clustering of RSFC patterns across the blind. Three main clades emerge, with differential connectivity to sensorimotor and frontal cortices. Subclades are marked with Roman numerals, and an average V1-RSFC map for the individuals in each subclade is shown. Color circles by participant numbers indicate frequent blindness etiologies (Retinopathy of prematurity - ROP, blue; microphthalmia, yellow) and unique behavioral traits (ambidextrous individuals, red; left-handedness, purple; and faint light perception as opposed to no light perception, green). Hierarchical clustering in the blind does not support linking blindness etiology or crude light perception to the similarity in V1 RSFC profile. With the exception of the two ambidextrous individuals being clustered together, no other qualitative pattern is evident linking blindness etiology or light perception to the similarity in V1 RSFC profiles. Participants 13 and 20, found on different subclades, are siblings who are blind because of genetic microphthalmia. Extended Data Figure 3-1 shows comparable hierarchical clustering in the sighted group, showing lower distances than in the blind. ***B***, The V1-RSFC correlation (similarity) structure between individuals based on which hierarchical clustering analysis was conducted. ***C***, V1-RSFC to the left inferior frontal cortex in the blind (and not in the sighted) is correlated to the duration of formal education, showing one environmental factor affecting individual differences in brain reorganization in blindness.

the clustering analysis, the average RSFC pattern (average V1-RSFC t map across the subjects) for individuals within each subclade was computed. The hierarchical clustering was also similarly conducted on individual maps derived from sighted participants. The distance values of lower nondiagonal elements of the dissimilarity matrix were statistically compared between the groups.

Correlation with education

As a preliminarily analysis to inspect the effect of specific environmental factors on V1 RSFC variability, we calculated the correlation between the V1-seeded RSFC of each voxel for all participants with the number of years of formal schooling they received for each group separately at the whole-brain level using a gray matter mask at $p < 0.05$ corrected (Fig. 3*C*, for the blind; the sighted showed no significant correlation). In the IFS cluster showing such correlation in the blind, correlation in the sighted group was also sampled.

Data availability

Study data are available on request from the corresponding author.

Results

V1 variability differs between congenitally blind and sighted individuals

We tested whether visual deprivation leads to altered interindividual variability in the connectivity patterns of the primary visual cortex in a large group of congenitally fully blind adults (n = 25; Table 1) and sighted adults (n = 31) from two experimental cohorts scanned previously (Striem-Amit et al., 2015, 2018b; each cohort contained a blind and matched sighted group). We computed RSFC from an anatomically defined seed in retinotopic primary V1, based on a visual localizer in an independent group of sighted individuals (Striem-Amit et al., 2015). To assess whether RSFC variability effects are indeed because of the absence of shared experience, the same procedures were computed for control seed regions in all nonvisual Brodmann areas.

We first tested whether there are differences in interindividual variability of the V1-seeded RSFC resulting from blindness. For this aim, RSFC maps were analyzed using ANOVA (cohort times group, to remove any cohort effects, in addition to relevant preprocessing steps; see above, Materials and Methods). As the cohort differences were negligible and highly localized (Fig. 2*B*,*C*), RSFC maps across cohorts within each group (blind, sighted) were analyzed for their voxel-wise variability across individuals. We calculated a whole-brain voxel-level homogeneity of variance test (Brown–Forsythe test; Brown and Forsythe, 1974; see above, Materials and Methods) for the group main effect, testing whether the two groups differed in their interindividual variability of the RSFC values. This analysis revealed multiple areas that exhibit a significant intersubject difference in V1-seeded RSFC variability between the blind and sighted groups (Fig. 1*A*; group variability difference). These included areas of the ventral and dorsal visual pathways, posterior inferior parietal cortex, and the inferior frontal cortex. Therefore, visual experience affects brain consistency. This analysis reveals only a

nondirectional difference in variability; to directly test the sign of the group difference, we calculated the ratio of variability between the groups (blind/sighted) across the brain (Fig. 1*B*, ratio shown within areas that differ in variability between the groups). It is apparent that the blind show higher variability than the sighted in multiple areas, including parietal and frontal regions, with lower variability in only one cluster in the right auditory cortex. Thus, visual experience can have an overall stabilizing effect on RSFC, and visual deprivation results in overall more variable RSFC from the visual cortex. This suggests a role of shared experience in promoting consistency of neural organization.

V1 variability increases especially for areas that reorganize in blindness

Inspecting interindividual variability also allowed us to test whether neural reorganization is consistent across blind individuals. Are areas whose connectivity and function have reorganized because of blindness also highly variable among blind individuals compared with the typical interindividual differences for these areas? We tested this by inspecting the intragroup variability difference in the areas showing a main effect of group in the V1-RSFC values; areas showing change in V1-seeded RSFC between the blind and sighted (a two-way ANOVA main group effect; Fig. 2*A*; Extended Data Fig. 1-1 shows replication of the results with global signal regression).

In accordance with previous work (Liu et al., 2007; Yu et al., 2008; Wang et al., 2014; Burton et al., 2014; Qin et al., 2015; Striem-Amit et al., 2015), group differences in functional connectivity were robust (Fig. 2*A*). Blind individuals showed increased functional connectivity to some regions in the visual cortex and several areas in the frontal lobe, including the inferior frontal sulcus (Fig. 2*D*). We sampled the areas showing a V1-RSFC group difference to inspect whether they would also show increased variability in the blind group. Indeed, variability of the RSFC to large regions in the ventral and dorsal streams was five times greater in blindness (Fig. 2*E*; ventral stream, $S^2_{sighted} = 0.86$, $S^2_{Blind} = 5.13$; dorsal stream, $S^2_{sighted} = 0.64$, $S^2_{Blind} = 4.15$). Curiously, variability of RSFC to the sensorimotor cortex, which showed reduced functional connectivity to the visual cortex in blindness was slightly decreased in the blind (left hemisphere, S^2 blind = 1.05, S^2 sighted =1.30, variance ratio 0.81; right hemisphere, S^2 blind = 0.63, S^2 sighted = 1.34; variance ratio 0.47), although the difference did not reach significance (Brown–Forsythe test, left hemisphere, $F = 0.75$; right hemisphere, $F = 0.96$; Fig. 2*E*).

Given the proposal that increased connectivity with the frontal cortex (Liu et al., 2007; Hawellek et al., 2013; Burton et al., 2014; Deen et al., 2015; Striem-Amit et al., 2015; Abboud and Cohen, 2019) drives reorganization in the visual cortex of the blind (Deen et al., 2015; Bedny, 2017; Abboud and Cohen, 2019; Rimmele et al., 2019), we tested RSFC variability in these foci within the group of blind participants. Inferior frontal areas that show increased RSFC in the blind show more than double the variability within the blind group as within the sighted group (Fig. 2*E*; $S^2_{sighted} = 1.21$, $S^2_{Blind} = 3.45$). To specifically test frontal regions proposed to affect visual cortex reorganization, we directly examined the variability of connectivity in left-lateralized frontal language regions. A spoken-language-selective region was defined in the left inferior frontal sulcus (from a contrast of responses to heard object names more than to heard pseudowords in a joint group of blind and sighted subjects from Striem-Amit et al., 2018b; see above, Materials and Methods). In this region as well, the intrablind RSFC-with-V1 variability was more than quadruple the intrasighted variability ($S^2_{sighted} = 1.00$, $S^2_{blind} = 4.39$; Fig. 2*F*). Therefore, it appears that reorganization in the connectivity between the visual and frontal cortex in the blind is highly variable among the blind individuals.

Is this a general pattern, that neural reorganization manifests more variably in blindness? We correlated the spatial pattern of the group difference in mean RSFC from the visual cortex seed (Fig. 2*D*) with the variability difference between the groups (Fig. 1*B*, computed within a gray matter mask). The concordance correlation coefficient between the two maps (Lin, 1989) was highly significant (CCC = 0.332, $p < 0.00{,}001$; using a permutation test shuffling the order of the voxels, 100,000 iterations; Fig. 2*G*). Therefore, it appears that when the brain reorganizes, it introduces a further source of variance, resulting in more diverse connectivity values. Importantly, the link between reorganization and variability is not an artifact because of the higher mean difference between the groups. Using group-normalized V1-RSFC values shows that the variability is increased in the blind even when controlling for the higher group mean value (Extended Data Fig. 1-2*A*,*B*) and when regressing out the global signal (Extended Data Fig. 1-1).

Next, we tested the specificity of the link between reorganization and increased variability. If this pattern is driven by visual deprivation, we expected it to be especially prominent for the primary visual cortex seed, compared with seeds in nonvisual areas. As a control, we performed the same analysis we performed on V1 in a whole-brain level via parcellation to Brodmann areas and used each of the nonvisual Brodmann areas (with the exception of areas 17, 18, 19, and 37) as a seed for RSFC variability analyses. Nonvisual regions did not show the same phenomena as V1. Specifically, there was a significantly less pronounced change to the variability of functional connectivity between the groups from nonvisual seed ROIs as compared with V1 (comparing number of significant voxels showing a significant variability change; $t_{(34)} = 21.55$, $p < 0.0001$). It is important to note that given the increased variability of connectivity from the early visual cortex to most other cortical areas, we expected a nonzero change in variability in nonvisual areas as well because their connectivity to at least the primary visual cortex is expected to increase. Moreover, nonvisual Brodmann areas did not show as significant a link between increased variability and reorganization. The correlation between the Brown–Forsythe map and the ANOVA main group effect was significantly lower than the corresponding correlation for V1 ($t_{(34)} = 60.97$, $p < 0.0001$). Further, we performed the correlation analysis between the group difference for V1 and the variability difference across the different seeds as a permutation test. The cross-seed correlation, the correlation between the group difference for V1 and the variability difference of any other Brodmann area computed in a gray matter mask, was close to zero (CCC = 0.0017; Fig. 2*H*), showing that the link between variability and reorganization is spatially specific. However, the difference between matched and permuted, cross-seed correlations was also significant for the nonvisual Brodmann areas ($t_{(68)} = 5.34$, $p < 0.0001$; Fig. 2*I*). This shows that although the link between the increase in variability and change in RSFC in the blind is much more pronounced in connectivity with the visual cortex, even more broadly, reorganization is correlated to greater variability. Overall, this suggests that visual cortex plasticity is characterized by increased variability and not by a ubiquitous change for all individuals.

Spatial patterns variability across blind individuals

What forms does this increased variability take? We further asked whether the plastic reorganization of visual cortex functional

connectivity (Liu et al., 2007; Yu et al., 2008; Wang et al., 2014; Deen et al., 2015; Striem-Amit et al., 2015; Abboud and Cohen, 2019) manifests in a stereotypical, similar change across blind individuals, or if it is spatially idiosyncratic. To inspect whether variability also manifests in different spatial patterns of connectivity in the blind, we used hierarchical clustering to group the blind individuals into clades based on their RSFC patterns and examined the RSFC pattern characterizing each subclade. This approach revealed informative diversity in the profiles of RSFC of the visual cortex among the blind individuals (Fig. 3*A*; Fig. 3*B* shows the correlation matrix underlying this clustering). Most of the blind individuals clustered together in a clade showing (on average) focused positive RSFC with foci in the inferior frontal cortex (IFC; clade 3, 17 individuals), along with differential patterns of RSFC with the superior frontal lobe: positive and negative values across individuals in different subclades (e.g., subclades III and V). Curiously, in most of these subclades, RSFC to the IFC was bilateral (subclades V and VII), whereas in a subclade of three individuals the pattern seemed lateralized to the left IFC (Fig. 3*A*, subclade VI). Given that functional connectivity to the left frontal cortex is the most drastic form of connectivity reorganization associated with blindness (Liu et al., 2007; Yu et al., 2008; Wang et al., 2014; Burton et al., 2014; Qin et al., 2015; Striem-Amit et al., 2015), which has been described driving it toward functionally processing language (Bedny, 2017), the rarity of its lateralization in blind individuals is curious.

Two additional smaller clades seemed to cluster separately based on RSFC with the sensorimotor and auditory cortices, with a small clade (clade 2, five individuals) showing negative RSFC (anticorrelation) with the sensorimotor cortex, and three individuals (clade 1) showing a pattern of positive RSFC with the sensorimotor cortex as well as with the auditory cortex. Although the sighted data also yielded a similar number of clades, its overall distances were lower ($t_{(52)} = 3.17$, $p = 0.007$; Extended Data Fig. 3-1). Interestingly, the clustering in the blind did not show any qualitative distinction based on blindness etiology (Fig. 3*A*), including a sparse distribution among

Gunnar, 2020). This emphasizes the importance of understanding plasticity through the lens of individual differences.

Here, we studied the role of a more extreme form of environmental change—complete deprivation of an entire sensory channel. We showed that experience has immense effects on individual differences and can modify the variability in the neural connectivity profile of extensive cortical tissue. In the past, functional connectivity variability was found to be highest in association cortices that developed phylogenetically recently (Kaas, 2006; Smaers et al., 2011; Krubitzer and Prescott, 2018), whereas sensory cortices exhibited low variability (Fischl et al., 2008; Mueller et al., 2013; Xu et al., 2018; Anderson et al., 2021). However, studying typically developed individuals does not allow us to resolve whether increased individual variability in these regions results from longer exposure to environmental factors in the individual's lifetime or from less tight genetic control for later developed phylogenetic regions allowing more diversity, as the two factors are typically confounded. Association networks develop through adolescence, whereas early sensorimotor systems mature earlier (Guillery, 2005; Shaw et al., 2008

individuals could lead to variability in visual system connectivity, as well as differential functional responses (van den Hurk et al., 2017; Abboud et al., 2019; Rosenke et al., 2020; Mattioni et al., 2020b). Here, we are unable to separate these two accounts completely. In a partial attempt to do so, we have shown here that the RSFC of the visual cortex to the left IFC is correlated to an individual's duration of formal education. However, most of the regions that showed changes in variability were not accounted for in this preliminary exploration. Furthermore, overall increased variability was not found in nonvisual sensory areas (auditory and somatosensory cortices), making it unlikely that experience or expertise in compensatory senses underlies the full variability. In fact, a cluster in the auditory cortex cortices showed decreased connectivity variability in blindness (similarly to a nonsignificant effect in the sensorimotor cortex; Fig. 2*E*), suggesting that the opposite effect, consistent reliance on audition in blindness, may also cause increased consistency of cross-modal connectivity. Future work should parse out the effects of specific environmental and personal factors affecting the postnatal reorganization in the blind.

Based on our exploratory clustering analysis, reorganization generates distinct spatial connectivity profiles. For example, connectivity between the visual and sensorimotor cortices varies between positive and negative values across individuals. This pattern suggests potentially informative changes in the link between the senses and the importance of reorganization regarding touch in different blind individuals. Most of the blind show connectivity between V1 and the IFC, but connectivity to the superior frontal cortex differs between subclades. Although a full characterization of individual profiles would benefit from additional correlates and an increased sample size, we can already gain two interesting insights. The first is that the most drastic form of reorganization associated with blindness, lateralized functional connectivity to the left frontal cortex (Liu et al., 2007; Yu et al., 2008; Wang et al., 2014; Burton et al., 2014; Qin et al., 2015; Striem-Amit et al., 2015), which has been described as allowing visual cortex functional recruitment for language (Bedny, 2017), is found only in a minority of the subjects (three of 25 participants; subclade VI; Fig. 3*A*). Overall, the RSFC between V1 and frontal cortex is quite variable (Figs. 1*B*, 2*E*,*F*) and more often bilateral (Figs. 2*D*, 3*A*). This observed heterogeneity of V1 connectivity can aid in resolving some of the current debate revolving the role of early visual cortex in blindness. The early visual cortex, at the group level, has shown recruitment in multiple tasks, including both low-level sensory processing and high-level cognitive functions (Sadato et al., 1996; Büchel et al., 1998; Weeks et al., 2000; Burton et al., 2002b; Amedi et al., 2003; Burton et al., 2004; Gougoux et al., 2005; Stilla et al., 2008; Bedny et al., 2011; Kanjlia et al., 2016; Mattioni et al., 2020a), challenging the definition of its functional role in blindness. This led to controversy about its capacity to plastically reorganize for nonvisual computations remote from its typical visual role (Bedny, 2017; Crollen et al., 2019; Seydell-Greenwald et al., 2020), as well as a debate on its place in the processing hierarchy (Amedi et al., 2003; Büchel, 2003; Watkins et al., 2012; Fine and Park, 2018). Beyond blindness, this debate has broader implications to the capacity for cortical plasticity also in other systems in congenital deafness (Lomber, 2017; Cardin et al., 2020) and handlessness (Hahamy et al., 2017; Striem-Amit et al., 2018a). Although our data cannot resolve this controversy, they offer an additional lens to inspect group-level data; it is possible that some of the contradictory group activations stem from different subgroups of blind participants (as seen in the ventral visual cortex; Rosenke et al., 2020) and that V1 in blindness may potentially assume different functional roles in different individuals. A similar approach may be further adopted to explain the variability found in functional recruitment profiles for the ventral visual cortex across individuals (van den Hurk et al., 2017; Rosenke et al., 2020; Mattioni et al., 2020b).

The spatial variability we report here can also interact with temporal variability. Recently, visual functional connectivity to the auditory cortex was shown to temporally vary more in blindness, as well as between task and rest (Pelland et al., 2017). This suggested that the visual cortex may not just take different roles across individuals as we propose here but may also vary its role and connectivity across time and tasks in a single blind person. Future studies will need to explore more deeply how individual differences manifest in blindness across different states and whether this information can aid in characterizing individual phenotypes (Greene et al., 2020). Different spatial RSFC patterns may reflect biases in engaging the visual cortex for longer durations in a specific functional network, even when no relevant task is attended, highlighting a more significant role for one function in each individual.

Importantly, studies in sighted individuals already show that individual differences can manifest across states (Gratton et al., 2018), allowing RSFC, even on its own, to be harnessed for predicting developmental outcomes (Kamps et al., 2020; Li et al., 2020; Whitfield-Gabrieli et al., 2020; Yu et al., 2021), clinical outcomes (Wisch et al., 2020; Prakash et al., 2021), and even therapeutic prescription (Fox and Greicius, 2010; Drysdale et al., 2017). Therefore, regardless of their sources, the existence of different reorganization profiles we observed may have clinical implications for vision rehabilitation. The causes of the high variability of outcomes of sight restoration attempts (Gregory and Wallace, 1963; Carlson et al., 1986; Ganesh et al., 2014; Huber et al., 2015) remain unknown, with some patients gaining little functional sight. As evident from cochlear implantation in deafness (Lee et al., 2001; Olds et al., 2016; Feng et al., 2018; cf. Lyness et al., 2013; Heimler et al., 2014; Land et al., 2016), variability in restoring a missing sense may depend on neural system retention as cross-modal reorganization may render it incapable of processing information of the original modality. Similarly, in visual restoration, some failed sight restoration attempts may have neural causes (Striem-Amit et al., 2011). In contrast to invasive methods that require an intact visual system, assistive and adaptive technologies such as sensory substitution devices are designed to use cross-modal translations. For example, sensory substitution devices that convert visual images into sounds or touch (Bach-Y-Rita et al., 1969; Meijer, 1992; Capelle et al., 1998; Striem-Amit et al., 2012) could benefit from cross-modal plasticity of specific senses (Brown et al., 2011; Arnold et al., 2017). In late-onset vision loss because of age-related diseases (e.g., macular degeneration, glaucoma, cataracts) there is a dizzying selection of sensory aids and substitution techniques. For the task of reading alone, approaches include refreshable Braille displays, screen readers, and optical and electronic aids using touch, audition, and vision, respectively. Similar diversity exists for navigation needs (guide dog, white cane, electronic canes, smart glasses). Matching technologies that are most effective based on the individual neural plasticity profile may aid in individually tailored, personalized medicine and assistive technology in sight rehabilitation of visual disorders.

In conclusion, we showed that in the absence of sensory experience because of blindness, brain reorganization generates larger interindividual variability beyond the individual differences

found in the typical sighted population. Variability is increased especially for areas that have reorganized in their connectivity to V1 because of blindness, and blind individuals show different spatial patterns of connectivity of their visual cortex. This finding suggests an important role for experience in determining the individual variability of neural organization. Additionally, these results highlight the need to consider idiosyncratic profiles of plasticity in tailoring rehabilitation plans for individuals with sensory deficits.

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