significant, dose-dependent, concentration-dependent, and visually evident changes in cardiac contractility as indicated by increases in FS (Fig. 4A and movie S1) (19).

Omecamtiv mecarbil improved left ventricular systolic function in a conscious canine model with chronically implanted sensors to assess LV dimensions, atrial and arterial pressures, and stroke volume (20). The direct effect on cardiac contractility was evident from the increase in myocardial wall thickening (WT) and FS (Fig. 4B) in the absence of a change in loading conditions, such as mean arterial pressure, LV end diastolic pressure, and total vascular resistance (−2.2 ± 1.3% , −7.3 ± 5.8% , and −2.4 ± 2.3%, means ± SEM, P > 0.05). In dogs with heart failure induced by chronic fast pacing of heart rate in concert with a localized myocardial infarction (21), omecamtiv mecarbil produced substantially greater and statistically significant (P < 0.01) increases in stroke volume (60.8 ± 12.5%) and cardiac output (29.1 ± 6.1%) than it did in normal dogs (10.2 ± 3.6% and 0.8 ± 2.0%, respectively). The increase in cardiac output was especially notable given the coincident lowering of heart rate (−16.7 ± 4.0%, P = 0.014) observed in the dogs with heart failure (Fig. 4B; P calculated using Student’s t-test).

Underlying the effects on systolic function was an increase in systolic ejection time (SET) in the absence of changes in the rate of LV pressure development (dP/dt) (Fig. 4B). In contrast, existing drugs, such as the β-adrenergic agonist dobutamine, increase cardiac contractility by increasing dP/dt and shortening SET (22). We investigated this finding further by comparing omecamtiv mecarbil with dobutamine, using time-dependent LV end systolic elastance, a load-independent measure of cardiac contractility derived from the pressure-volume loop (23). The plots of time-dependent elastance (Fig. 4C) are illustrative of the different effects that the two drug mechanisms have on the dynamics of cardiac contractility.

Overall energy balance in the contracting heart is set by a combination of loading conditions, heart rate, membrane ion fluxes, calcium cycling, and crossbridge cycling. Although omecamtiv mecarbil might increase ATP turnover at the level of the sarcomere, on balance, myocardial energetics appear unchanged following omecamtiv mecarbil administration, as it does not increase overall myocardial oxygen consumption (8) at doses producing substantial improvements in cardiac function. However, excessive crossbridge activation at excessive doses of omecamtiv mecarbil could lead to an increase in the duration of systole to an extent where coronary blood flow during diastole is reduced, and signs and symptoms of cardiac ischemia may emerge.

As a selective, allosteric activator of cardiac myosin, omecamtiv mecarbil is a rare example of a drug mechanism whose action depends on activation rather than inhibition of an enzyme, an approach that may have broader application for therapeutic intervention (24–26). It represents a therapeutic approach to directly improve cardiac function that potentially avoids the deleterious effects limiting current indirect inotropic mechanisms (27). Further studies in patients with heart failure will eventually define the clinical benefit and risk profile of cardiac myosin activation in a condition that is still marked by substantial rates of mortality and morbidity.

References and Notes
8. Y. T. Shen et al., Circ Heart Fail. 3, 522 (2010).
9. Materials and methods are available as supporting material on Science Online.
16. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
19. In the online materials, a side-by-side movie shows several heatbeats of a short-axis echocardiogram in an anesthetized beagle before (on the left) and after (on the right) a 1-hour infusion of omecamtiv mecarbil at 1 mg/kg of body weight per hour. In this view, the left ventricular cavity is in the middle of a ring of contracting myocardi um.
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Supporting Online Material
www.sciencemag.org/cgi/content/full/331/6023/1439/DC1
Materials and Methods
Fig. S1 to S9
Tables S1 to S3
References
Movie S1
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Reversal of Interlaminar Signal Between Sensory and Memory Processing in Monkey Temporal Cortex
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The primate temporal cortex implements visual long-term memory. However, how its interlaminar circuitry executes cognitive computations is poorly understood. Using linear-array multicontact electrodes, we simultaneously recorded unit activities across cortical layers in the perirhinal cortex of macaques performing a pair-association memory task. Cortical layers were estimated on the basis of current source density profiles with histological verifications, and the interlaminar signal flow was determined with cross-correlation analysis between spike trains. During the cue period, canonical “feed-forward” signals flowed from granular to supragranular layers and from supragranular to infragranular layers. During the delay period, however, the signal flow reversed to the “feed-back” direction: from infragranular to supragranular layers. This reversal of signal flow highlights how the temporal cortex differentially recruits its laminar circuits for sensory and mnemonic processing.

The primate inferotemporal cortex locates at the final stage of the ventral visual pathway and serves as a storehouse for visual long-term memory (1–4). Previous studies have demonstrated neuronal activity related to presented visual objects and retrieved images at the single-neuron level (4–6), but the underlying network dynamics (7–12) remain to be understood. Evidence from the primary sensory cortices suggests that local circuits extending across cortical layers are crucially involved in sensory processing (13–15).

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This raises questions about how the interlaminar circuitry in the inferotemporal cortex is differentially recruited to process presented objects and to retrieve visual long-term memory.

We used two strategies to investigate interlaminar signal flow in awake behaving monkeys. First, we used current source density (CSD) analysis as a tool for layer estimation in each electrode penetration; CSD reflects the gross transmembrane currents in the local neuronal ensemble and is used to estimate the cortical layers that receive afferent inputs (16, 17). Second, we used cross-correlation analysis of spike trains (18–21) to infer the functional interactions across cortical layers; asymmetry or peak lag of the cross-correlogram (CCG) reflects the direction of functional connectivity between neurons (22, 23).

Two monkeys were trained to perform a pair-association task, in which they had to retrieve the learned paired associate in response to the presented cue stimulus (Fig. 1A) (3–5). We recorded single- and multi-unit activities and local field potentials (LFPs) by inserting linear-array multicontact electrodes (16 or 24 contacts with spacing of 150 or 100 μm, respectively) vertically (table S1) (24) into area 36 (A36) (Fig. 1B). CSD was then calculated from depth profiles of stimulus-evoked LFPs in order to physiologically estimate the position of the granular layer (24). A representative CSD profile exhibited the earliest current sink (Fig. 1, D and E, asterisks) at the contact corresponding to the histologically verified granular layer (Fig. 1C, red). This earliest current sink was followed by sinks at more superficial contacts and by sources at deeper contacts (Fig. 1D). Similar CSD profiles were consistently observed for all penetrations (fig. S1). Postmortem histological analyses (24) confirmed that the earliest current sink evoked by cue stimuli consistently corresponded to the granular layer [table S1, the distance between the contact with the earliest current sink (“earliest-sink contact”), and the center of the granular layer was 79 μm (median), n = 6 penetrations]. The histological verifications, together with consistent CSD profiles across penetrations, demonstrated that the CSD profiles can be reliably used to estimate the granular layer (G), the supragranular layer (SG), and the infragranular layer (IG) (24). In this representative penetration, single unit activities were simultaneously recorded in SG and IG (Fig. 1, F and G), both showing stimulus-selective responses during the cue period (Fig. 1H). The CCG (18–23) for this unit pair exhibited a significant displaced peak (4 ms lag) on the right side (Fig. 1I), suggesting a functional connectivity from the SG unit to the IG unit, which is consistent with the “feed-forward” signal flow in the primary sensory cortices (13–15).

We made 20 penetrations in three hemispheres of two monkeys and conducted cross-correlation analyses for three populations of unit pairs: G-SG pairs (cue period, n = 52 pairs; delay-period, n = 49 pairs), G-IG pairs (n = 128 pairs; n = 121 pairs), and SG-IG pairs (n = 252 pairs; n = 211 pairs) [both single units and multi-units were included; for details, see supporting online material (SOM) text and table S2]. A CCG was calculated only when both constituent units responded to at least one common stimulus during either the cue or delay period. CCG peak was detected within 10 ms lag (19–22) so as to evaluate its significance (Z > 2.82, P < 0.05) (24). We then compared the proportions of unit pairs with significant CCG peaks among the G-SG, G-IG, and SG-IG pairs (fig. S2). The proportion of unit pairs with a significant CCG peak was greater for G-SG pairs than for G-IG pairs during both the cue period (33% versus 11%; χ² test with post-hoc pair-wise comparisons followed by Bonferroni’s correction, P < 0.005) and delay period (27% versus 12%; P < 0.05). The proportion of unit pairs with a significant CCG peak was greater for G-SG pairs than for SG-IG pairs during the cue period (33% versus 16%;
Asymmetry Index

Proportion of pairs (%) 10-10

-5

0

5

10

-5

0

5

10

Fig. 2. Population results of the functional connectivity. (A to C) Cross-correlation between spike trains of G-SG pairs. (A) Population-averaged CCGs in the (gray, left) fix, (blue, middle) cue, and (red, right) delay periods, respectively. (B) Asymmetry index and (C) center of mass of individual CCGs. Asterisk indicates significant bias to either side of the histogram. Filled histogram indicates a task period for which significant bias in the directionality was observed. (D) Schematic diagram of interlaminar signal flow between G and SG. (E to H) Same as in (A) to (D), but for SG-IG pairs.
positions of units by parametrically using the distances from the estimated granular layer (Fig. 4 and fig. S8) (25, 26). Compared with the connectivity during the fix period, two prominent connectivity patterns appeared during the cue period, corresponding to the feed-forward pathways from G to SG and from SG to IG (Fig. 4, A and B, middle). During the delay period, the feed-forward connectivity was attenuated, and the feed-back connectivity from IG to SG emerged (Fig. 4, A and B, right). In addition, outward signal flow (from superficial to deep parts) within IG was found during the delay period (Fig. 4, A and B, right). Putative target units of this outward flow were located at significantly deeper positions than those of the putative source.

**Fig. 3.** Connectivity dynamics of individual SG-IG pairs. (A) Time course of spike correlation for individual unit pairs. AI and CS of CCGs were color-coded as shown in the inset. Unit pairs were sorted according to AI value during the latter half of the delay period. (B) Population average of all the unit pairs. (C and D) Polar plot of CS and AI dynamics for the (C) flipped- and (D) non-flipped pairs. Radius, CS. Angle from the vertical axis, AI. Positions of base and tip of an arrow correspond to AI/CS values during cue and delay periods, respectively. (C), right) Proportion of each type of flipped pairs. S and I represent SG and IG, respectively. (D), right) AI of non-flipped pairs during the cue and delay periods. Blue, SG→IG pairs; orange, IG→SG pairs.

**Fig. 4.** Interlaminar connectivity matrices. (A) AI matrix for each task period. Abscissa and ordinate represent recorded positions of the putative source and target units relative to the earliest-sink contact, respectively. Size of a circle in each matrix indicates the proportion of unit pairs with significant CCG peak to the total number of unit pairs for which CCGs were calculated at the corresponding site. Saturation of color of each circle indicates the average of AI across unit pairs. (B) CS matrix, as in (A). All laminar positions plotted in the AI and CS matrices were recorded in at least three penetrations. (C) Summary diagrams showing all the laminar signal flows identified in the present study.
A Brief Social-Belonging Intervention Improves Academic and Health Outcomes of Minority Students

Gregory M. Walton1* and Geoffrey L. Cohen1,2

A brief intervention aimed at buttressing college freshmen’s sense of social belonging in school was tested in a randomized controlled trial (N = 92), and its academic and health-related consequences over 3 years are reported. The intervention aimed to lessen psychological perceptions of threat on campus by framing social adversity as common and transient. It used subtle attitude-change strategies to lead participants to self-generate the intervention message. The intervention was expected to be particularly beneficial to African-American students (N = 49), a stereotyped and socially marginalized group in academics, and less so to European-American students (N = 43). Consistent with these expectations, over the 3-year observation period the intervention raised African Americans’ grade-point average (GPA) relative to multiple control groups and halved the minority achievement gap. This performance boost was mediated by the effect of the intervention on subjective construal: It prevented students from uncertain about their social belonging in mainstream institutions like school and work (7). Because their ethnic group is often negatively stereotyped and marginalized, they may be unsure of whether they will be fully included in positive social relationships in these settings (2). As the sociologist Erving Goffman wrote, “The central feature of the stigmatized individual’s situation in life...is a question of...acceptance” (15). Uncertainty about belonging, especially when chronic, can undermine minorities’ performance (7, 16) and health (3, 17, 18). Social belonging may thus constitute a psychological lever where targeted intervention could yield broad benefits.

A n important question facing society concerns the origins of inequalities between socially marginalized and nonmarginalized groups. Among the most consequential of inequalities is the poorer school and health outcomes experienced by African Americans, Latino Americans, and other non-Asian ethnic minorities relative to European Americans. These differences occur at all levels of socioeconomic status (1–3).

Although many structural factors contribute to these inequalities, the present research examin-