tion of this gene. Identification of the *LIS-1* gene should therefore prove useful in the study of neuronal migration in normal development as well as in this unique human disorder. □

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1. Aicardi, J. *Int. Pediatr.* **4,** 118–126 (1989).
2. Dobyns, W. B. *Neurol. Clin.* **7,** 89–105 (1989).
3. Barth, P. G. *Can. J. Neurol. Sci.* **14,** 1–16 (1987).
4. Miller, J. Q. *Neurology* **13,** 841–850 (1963).
5. Dieker, H. *et. al. The Lissencephaly Syndrome. The Clinical Delineation of Birth Defects II: Malformation Syndromes* 1–64 (National Foundation March of Dimes, New York, 1969).
6. Ledbetter, S. A., Kuwano, A., Dobyns, W. B. & Ledbetter, D. H. *Am. J. hum. Genet.* **50,** 182–189 (1992).
7. Duronio, R. J., Gordon, J. I. & Boguski, M. S. *Proteins* **13,** 41–56 (1992).
8. Lee, C. C. *et al. Science* **239,** 1288–1291 (1988).
9. Guillemot, F., Billault, A. & Auffray, C. *Proc. natn. Acad. Sci. U.S.A.* **86,** 4594–4598 (1989).
10. Guzzetta, V. *et al. Genomics* **13,** 551–559 (1992).
11. Dobyns, W. B., Curry, C. J. R., Hoyme, H. E., Turlington, L. & Ledbetter, D. H. *Am. J. hum. Genet.* **48,** 584–594 (1991).
12. Ledbetter, D. H. *et al. Proc. natn. Acad. Sci. U.S.A.* **86,** 5136–5140 (1989).
13. Leberer, E., Dignard, D., Hougan, L., Thomas, D. Y. & Whiteway, M. *EMBO J.* **11,** 4805–4813 (1992).
14. Birnbaumer, L. *Cell* **71,** 1069–1072 (1992).
15. Simon, M. I., Strathmann, M. P. & Gautam, N. *Science* **252,** 802–808 (1991).
16. Gilman, A. G. *A. Rev. Biochem.* **56,** 615–649 (1987).
17. Kleuss, C., Scherubl, H., Hescheler, J., Schultz, G. & Wittig, B. *Science* **259,** 832–834 (1993).
18. Iniguez–Lluhi, J. A., Simon, M. I., Robishaw, J. D. & Gilman, A. G. *J. biol. Chem.* **267,** 23409–23417 (1992).
19. Bourne, H. R. & Nicholl, R. *Cell* **72,** 65–76 (1993).
20. Igarashi, M., Strittematter, S. M., Vartanian, T. & Fishman, M. C. *Science* **259,** 77–79 (1993).
21. Nishimoto, I. *et al. Nature* **362,** 75–79 (1993).
22. Keleher, C. A., Redd, M. J., Schultz, J., Carlson, M. & Johnson, A. D. *Cell* **68,** 709–719 (1992).
23. Orikin, S. H. & Nathan, D. G. *New Engl. J. Med.* **295,** 710–714 (1976).
24. Altschul, S. F., Gish, W., Miller, W., Myers, E. W. & Lipman, D. J. *J. molec. Biol.* **215,** 403–410 (1990).
25. Bilofsky, H. S. & Burks, C. *Nucleic Acids Res.* **16,** 1861–1864 (1988).
26. vanTuinen, P., Rich, D. C., Summers, K. M. & Ledbetter, D. H. *Genomics* **1,** 374–381 (1987).
27. Sambrook, S., Fritisch, E. I. & Maniatis, T. *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory Press, New York, 1989).
28. Kuwano, A., Ledbetter, S. A., Dobyns, W. B., Emanuel, B. S. & Ledbetter, D. H. *Am. J. hum. Genet.* **49,** 707–714 (1991).
29. Kuwano, A. *et al. Hum. molec. Genet.* **1,** 417–425 (1992).

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Spectral motion produces an auditory after-effect

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DISTORTIONS of perception following prolonged exposure to an unvarying sensory stimulus have been observed since at least the third century BC[1]. The motion after-effect is a familiar experience[2] in which, after a few minutes of viewing objects moving in a single direction, a stationary object appears to move in the opposite direction. Similar after-effects have been observed for many visual stimuli, including tilted lines, colours, stereoscopic depth, curvature, spatial frequency, contrast, rotation and motion in depth[3–9]. In contrast to the rich variety of visual after-effects reported since the 1960s, reports of analogous auditory adaptation effects only appeared in the 1970s[10–12], but have continued since then[13,14]. Some effects of sound source spatial movement perception after adaptation to a spatially moving sound source have been reported[15]. Here we report an auditory perceptual after-effect analogous to the visual motion after-effect, which is caused by adaptation to auditory spectral (frequency) motion. After a few minutes of listening to a simple spectral pattern moving upwards or downwards in frequency space, the same pattern sounds as though it is drifting in the opposite direction when it is stationary. The effect shows binaural transfer, implying that it is generated at the level after binaural interaction. After-effects produced by the motion of spectral peaks are independent of those produced by spectral notches, suggesting separate processing channels for spectral peaks and notches.

The stimulus had a broad band, flat, noise spectrum on which was superimposed either a peak of narrow band noise, centred on a given frequency, or a narrow band notch. likewise centred on a given frequency (Fig. 1). The centre frequency of the peak or notch moved either upwards or downwards in frequency space, at a constant velocity, and with a repetitive sawtooth pattern. A two-alternative forced choice procedure was used to measure the after-effect of adaptation to this spectral motion. After 2–3 minutes of exposure to an adapting stimulus, the listener was asked to judge the direction of motion (up or down in frequency) of a briefly presented (0.5 s or less) test stimulus. Each test stimulus could have one of seven different velocities,

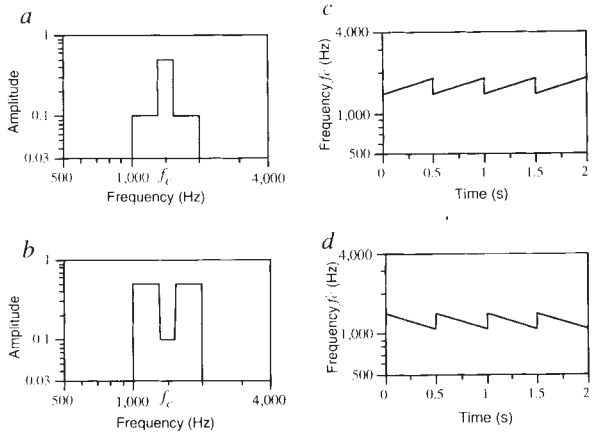

FIG. 1 Instantaneous amplitude spectra of the moving peak (*a*) and notch (*b*) stimuli, and the time functions of the central frequency of the peak or notch (*c* and *d*). The stimulus had a broad band, flat, noise spectrum on which was superimposed either a peak of narrow band noise, centred on frequency f_c, or a narrow band notch in the spectrum, also centred on f_c. f_c moved either upwards (c) or downwards (*d*) in frequency, at a constant velocity in log frequency space, and in a repetitive sawtooth pattern. The initial value of f_c was logarithmically centred in the frequency band of 1 to 2 kHz. The peak or notch was about 200 Hz wide and more than 15 dB above or below the baseline, which was kept constant during stimulus presentation. The velocities used in the briefly presented test stimuli were always slow enough that f_c did not cross the boundaries of the 1–2 kHz band during the test stimulus interval.

METHODS. The sound signals were computed digitally by two Motorola DSP56001 microprocessors in a Macintosh II computer. The sampling rate was 14,700 Hz, and the additive synthesis method was used. Sixty-four sinusoidal components with randomized initial phases were synthesized using the table look-up method with fractional phase steps and a table size of 1,024. Analogue voltages generated by the DSP boards were passed to a stereo amplifier (NAD Electronics, London) and presented to the subject by electrostatic headphones (Stax Industries, Tokyo).

chosen at random on each trial. Following each test, the adapting stimulus was presented again for 2 s to maintain the adaptation. A total of about 100 test and reinforcing presentations was given on each test of adaptation. The range of test velocities was always centred on zero and was chosen so that the extremes of the range were nearly always correctly identified by the subject

as moving up or down. Probit analysis[16] was used to estimate the 50% response rate on the resulting psychometric function. This is the stimulus velocity which sounded stationary to the listener (unchanging in pitch). A significant change in this subjective mean following adaptation indicates the presence of an after-effect.

In the first three experiments we examined the after-effect using either similar or different adapting and test stimuli. In experiment 1 we measured the after-effect obtained when the adapting and test stimuli were both moving peak stimuli (Fig. 1*a*). Different adapting velocities were used to examine their effects on the size of the after-effect. All subjects showed significant changes in the estimated subjective mean velocities after adaptation as compared with that of the control experiment (Fig. 2*a*). When the adapting velocity was positive, that is, upwards in frequency, the subjective mean velocity changed in a positive direction. Thus a positive velocity was judged by listeners as stationary and correspondingly a stationary velocity was heard as moving downwards. At negative adapting velocities, a moving peak stimulus with a negative velocity was also judged as stationary. The after-effects were maximum at adapting velocities of around ± 0.5 octaves per s.

For experiment 2, a different spectral pattern was used. At any given instant during presentation, both the adapting and the test stimuli had a notch in an otherwise flat spectrum over the same frequency band as that used above (Fig. 1*b*). The bandwidth of the notch was 200 Hz, the same as that of the peak in the first experiment. The centre frequency of the notch moved up or down in frequency space and, as before, the task of the listener was to judge the direction of motion of the notch in the test stimuli. All subjects showed significant after-effects following adaptation for adapting velocities around ± 0.5 octaves per s. In Fig. 2*b* the size of the after-effect is plotted as a function of the adapting velocity. The results were similar to those of experiment 1: after adapting to upward motion of a moving notch, a stationary notch appeared to move downwards, and vice versa.

To test whether adaptation to moving peaks and notches involved the same processing channels (experiment 3), we adapted first to a moving peak and then tested with a notch, and vice versa (cross-adaptation). The flat background level of the adapting stimulus and that of the test stimulus were kept the same. Figure 2*c* and *d* show the effect of adapting velocity on the subjective mean velocity of the test stimulus. Although there was some evidence for a weak effect of adaptation to a moving peak when tested with a notch stimulus, cross-adaptation generally produced effects that were weak or arguably non-existent. This suggests that after-effects produced by moving peaks and notches occur in different sensory channels.

In the visual system, after-effects thought to have a central locus typically show transfer between the two eyes (such as the motion after-effect), whereas after-effects that involve peripheral mechanisms (such as coloured after-images) do not transfer. To test whether the auditory after-effect is monaural or involves binaural pathways we adapted one ear and tested with the other ear. Figure 3 shows the size of interaural transfer of the after-effect as a function of adapting velocity. The after-effects for interaural transfer and same-ear adaptation were similar, suggesting that they are generated after the site of binaural interactions in the nervous system, and ruling out peripheral mechanisms for the after-effect.

These results suggest that the auditory system has a previously unsuspected sensitivity to the motion of peaks and troughs in the spectrum of complex sounds, extending the analogy between position on the basilar membrane of the cochlea and the position on the retina. Sensitivity to shape cues in the sound spectrum is an important factor in monaural sound localization[17–19]. The filtering effects of the head, pinna and the ear canal are substantial and complex, and result in changes in the spectral content of incoming sounds that are dependent on the incidence angle of the sound wavefront relative to the head. Such spectral cues

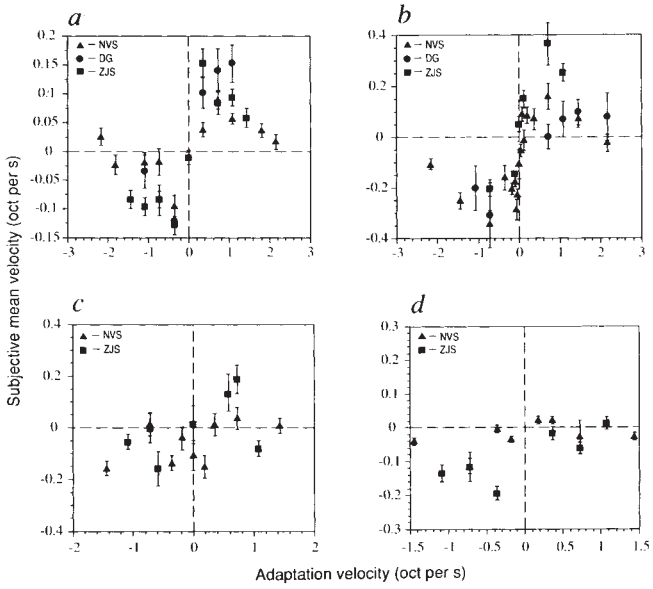

FIG. 2 Size of the monaural adaptation after-effect (in terms of the subjective mean velocity at which the stimulus sounded stationary) as a function of the velocity of the central frequency of the peak or notch in the adapting stimulus. Error bars indicate one s.d. in the mean, as estimated by the Probit procedure. Three listeners (N.V.S., D.G. and Z.J.S.) conducted these experiments. *a*, The listeners adapted to, and were tested with, moving peak stimuli; *b*, both the adapting and test stimuli were moving notches; *c*, the adapting stimulus was a moving peak whereas the test stimuli were moving notches; *d*, the adapting stimulus was a moving notch whereas the test stimuli were moving peaks. See text for details of the experiments, and Fig. 1 for the stimuli.

for monaural localization are thought to be important in locating the elevation of sound sources, which cannot be done using purely binaural cues, and may rely on detection and discrimination of spectral peaks and notches[20].

If, as seems likely, the auditory motion after-effect reported here is a consequence of changes of activity within populations of neurons selectively sensitive to spectral motion, the results of experiment 3 suggest that different neuronal populations encode the motion of peaks and notches in auditory stimuli. In addition, if sound frequency is analogous to space in visual perception, our finding of an after-effect for motion peaks or notches in

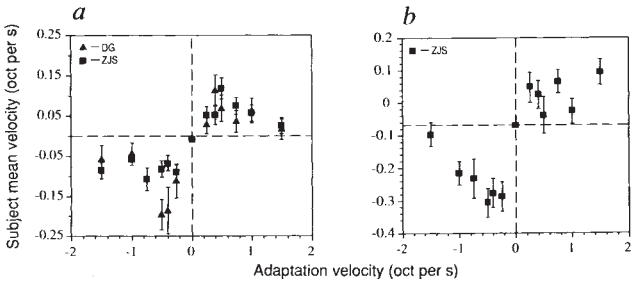

FIG. 3 Size of interaural transfer of the after-effect (in terms of the subjective mean velocity at which the stimulus sounded stationary) as a function of the velocity of the central frequency of the peak or notch in the adapting stimulus. In this case one ear was adapted and the other ear tested. Crosstalk between the two ears in our system was carefully checked to ensure that stimulation in the adapting ear was inaudible in the test ear. Error bars indicate one s.d. in the mean, as estimated by the Probit procedure. *a*, The adapting and test stimuli were both moving peaks; *b*, the adapting and test stimuli were both moving notches.

frequency space is simply an extension of the well known visual motion after-effect to another sensory domain. By analogy there may be neurons in the auditory pathways that are sensitive to the motion of spectral patterns, implying the existence of the auditory equivalent of dark and light bar detectors in the visual system. The results of interaural transfer suggest that these detectors are located at a level after binaural interaction. Although there is evidence for neurons sensitive to the motion of frequency peaks[21] there are as yet no reports of neurons sensitive to moving spectral notches, or even stationary gaps in the spectrum. There is evidence that spatial auditory source movement can be sensitively signalled by binaural temporal disparities in frequency-modulated signals[13], however this is likely to involve mechanisms other than those that detect changing frequency[22]. Our results suggest that further attempts to define such channels with neurophysiological and psychophysical methods would be worthwhile. □

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1. Aristotle *Parva Naturalia*.
2. Wohlgemuth, A. *Brit. J. Psychol.* **1,** 1–117 (1911).
3. Barlow, H. B. & Hill, R. M. *Nature* **200,** 1345–1347 (1963).
4. Sekuler, R. W. & Ganz, L. *Science* **139,** 419–420 (1963).
5. Anstis, S. M. *Science* **155,** 710–712 (1967).
6. Mayhew, J. E. W. & Anstis, S. M. *Percept. Psychophys.* **12,** 77–85 (1972).
7. Walker, J. T. *Psychonom. Sci.* **28,** 333–335 (1972).
8. Potts, M. J. & Harris, J. P. *Vision Res.* **15,** 1225–1230 (1975).
9. Favreau, O. E. *Vision Res.* **16,** 181–186 (1976).
10. Kay, R. H. & Matthews, D. R. *J. Physiol., Lond.* **225,** 657–677 (1972).
11. Regan, D. & Tansley, B. W. *J. Acoust. Soc. Am.* **65,** 1249–1257 (1979).
12. Gardner, R. B. & Wilson, J. P. *J. Acoust. Soc. Am.* **66,** 704–709 (1979).
13. Kay, R. H. *Physiol. Rev.* **62,** 894–975 (1982).
14. Wilson, J. P., Crampin, E. J. & Cann, N. *Brit. J. Audiol.* **26,** 188 (1992).
15. Grantham, D. W. *Percept. Psychophys.* **45,** 129–136 (1989).
16. Finney, D. J. *Probit Analysis* 3rd edn (Cambridge Univ. Press, 1971).
17. Blauert, J. *Spatial Hearing* (MIT Press, Cambridge, MA, 1983).
18. Bloom, P. J. *J. Audio. Eng. Soc.* **25,** 560–565 (1977).
19. Butler, R. A. & Helwig, C. C. *Am. J. Otolarybgol.* **4,** 165–173 (1983).
20. Moore, B. C. J., Oldfield, S. R. & Dooley, G. J. *J. Acoust. Soc. Am.* **85,** 820–836 (1989).
21. Mendelson, J. R. & Cynader, M. S. *Brain Res.* **327,** 331–335 (1985).
22. Green, G. G. R., Heffer, R. J. S. & Ross, D. A. *J. Physiol., Lond.* **260,** 49P (1976).

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Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state

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BRAIN cholinergic neurons are critical for memory function[1,2] and their loss may contribute to memory impairment in Alzheimer's disease[3]. One role of cholinergic neurons is to elicit an oscillatory activity called theta rhythm[4] in the hippocampus, a brain region involved in memory processing[5]. Theta rhythm occurs during periods of learning[6,7], but its effect on the synaptic plasticity that underlies learning remains unclear. We have studied synaptic plasticity in hippocampal slices during theta-frequency oscillations induced by a cholinergic agonist[8–10]. Here we report that during these oscillations, synapses are in a state of heightened plasticity and can be modified by what would otherwise be ineffective stimulation. This heightened plasticity is sensitive to the timing of incoming stimuli with respect to the oscillatory activity. The results suggest that cholinergic systems may affect memory formation through the induction of an oscillatory state in which the requirements for synaptic plasticity are dramatically altered.

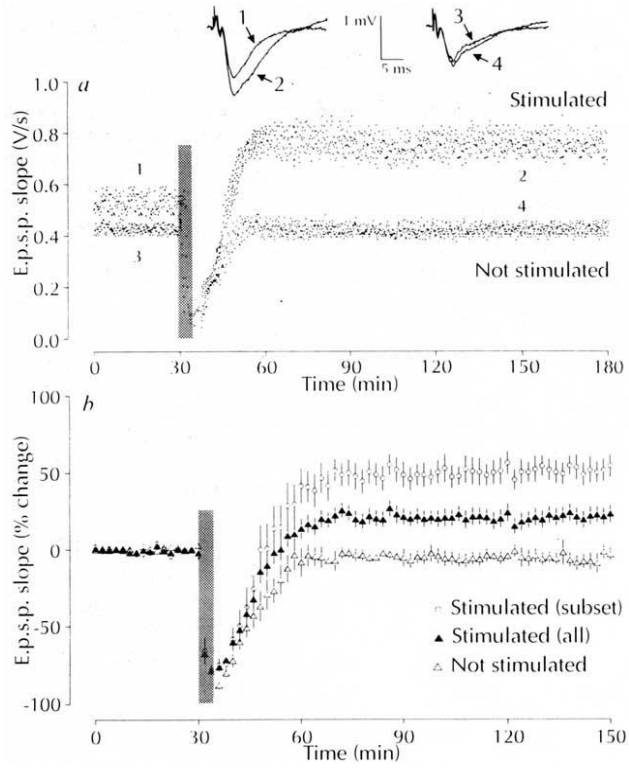

FIG. 1 Cholinergically induced long-term enhancement of synaptic efficacy. *a*, Representative experiment showing the slope of the field e.p.s.p. against time. During bath application of CCh (50 μM for 5 min, hatched rectangle), one pathway was stimulated and another pathway was not. Theta-frequency oscillations (mean amplitude, 280 μV) were present during CCh, but stimulation was not synchronized with the oscillations. Inset, field e.p.s.ps (average of 6 traces) taken at the times indicated by the numbers in the graph. *b*, Pooled data ($n = 27$) showing the average per cent change of the field e.p.s.p. in two pathways; synapses that were stimulated (▲) and synapses that were not stimulated (△) during CCh. Also shown are results from the stimulated pathway in the subset of experiments ($n = 10$) that showed large (>100 μV) theta-frequency oscillations during CCh (○). Symbols represent mean change (±s.e.m.) plotted at 2-min intervals (intervening data have been omitted for clarity). Similar results were obtained for the population spike amplitude concurrently recorded in stratum pyramidale in a subset of experiments: neurons that were stimulated during CCh were persistently enhanced (49 ± 4%, $n = 23$, $P < 0.001$, not shown).

METHODS. Transverse hippocampal slices (400 μm) were obtained from 100–250 g (2–8 weeks old) male Long-Evans rats[29] and maintained in a submerged chamber with continuous perfusion of oxygenated solution (in mM): NaCl, 124; NaH_2CO_3, 26; D-glucose, 10; KCl, 5; $CaCl_2$, 2; $MgSO_4$, 2; NaH_2PO_4, 1.2 (pH 7.4) at 30–32 °C. An extracellular recording microelectrode (2 M NaCl, 1–3 MΩ) was placed in stratum radiatum, 150–250 μm from stratum pyramidale. Recordings were made with an Axoclamp 2A amplifier. Evoked responses were sampled at 10 KHz and analysed on-line to determine the field e.p.s.p. initial slope. Two bipolar Pt/Ir microelectrodes were placed onto Schaffer collateral axons (at opposite sides of the recording microelectrode) and delivered current stimuli (0.1–0.5 mA, 50 μs) to elicit half-maximal response; stimuli were alternated so that a response was recorded every 5 seconds. To ensure independent stimulation of two sets of synapses, a paired-pulse facilitation paradigm (inter-stimulus interval of 50 ms) was used. Summary graphs were constructed by: (1) normalizing each experiment, by expressing all values as percentages of the mean value before CCh application, (2) aligning them with respect to the onset of CCh, and (3) averaging the time-matched, normalized data across experiments. The per cent changes quoted in the text (mean change ± s.e.m.) were obtained from the summary data by comparing the distributions of 18 averaged values during two 3-min intervals, one just before CCh application and the other 2 h after CCh application. Statistical significance, *P*, of this per cent change was computed using an unpaired Student *t*-test.