This scientific commentary refers to ‘Neuroanatomical precursors of dyslexia identified from pre-reading through to age 11’ by Clark et al. (doi:10.1093/brain/awu229).

Longitudinal research studies that follow at-risk samples before a disorder is evident, ideally from infancy, are the gold standard in the field of neurodevelopmental disorders (Goswami, 2014). They are also the rarest. In this issue of Brain, Clark and colleagues report a longitudinal structural neuroimaging study of children at high versus low risk of dyslexia that began before reading instruction commenced. The structural scans were taken the year before reading was taught (at age 6), a year after reading tuition began (at age 8), and after dyslexia had been diagnosed (at age 11). Clark et al.’s study thereby reveals the neurodevelopmental trajectory of the dyslexic brain, the only sure means of disentangling cause from effect in the aetiology of a neurodevelopmental disorder.

Longitudinal studies are crucial because the acquisition of reading is one of the most complex cognitive feats that the brain achieves. As young children learn to recode print to sound, the brain undergoes intensive and highly specific experience-dependent learning, often on a daily basis. These learning experiences selectively train aspects of sensory processing and attention. For example, oculomotor control and small shifts of visuospatial attention may be practised for hours every day. Learning to read literally changes the brain. Therefore, the identification of pre-reading weaknesses in neural structures and processes is vital to understanding causation in developmental dyslexia.

Clark and colleagues followed Norwegian children from preschool until sixth grade, identifying participants at high risk of dyslexia on the basis of family risk. They also followed a matched sample of children at low risk for dyslexia. The children's neurocognitive skills were assessed yearly. Norwegian is a relatively transparent orthography, and reading instruction commences at age 7. Most 7-year-olds quickly attain high efficiency in recoding print to sound (reaching >90% accuracy in reading words or pseudowords within the first year of schooling). However, the children who were later identified as dyslexic in Clark et al.’s study showed slow and inefficient learning of letters even as pre-schoolers, and showed severe impairments in recoding print to sound once reading instruction began. These neurocognitive profiles are very typical in dyslexia.

Previous structural and functional imaging studies of children and adults with dyslexia have consistently identified a left-lateralized network of brain regions that are believed to constitute the ‘reading network’ (Turkeltaub et al., 2003). Studies reveal extensive activation in brain areas related to audition, vision, language, spatial and cross-modal processing (e.g. posterior superior temporal cortex, occipitotemporal cortex, temporal and parietal areas, inferior frontal gyrus). As expertise in reading grows, activation that is initially bilateral becomes left-lateralized, and more focused on the occipitotemporal and posterior superior temporal cortices. Remarkably, Clark et al. did not find structural differences in any of these neural regions in their pre-reading scans.

Instead, the pre-reading neuroanatomical regions that differed significantly in cortical thickness were all in sensory areas, specifically primary auditory cortex (Heschl’s gyrus), primary visual cortex (lingual gyrus, V2), and some areas of frontal and cingulate cortex. These data suggest that sensory processing and possibly some elements of executive control already differ between children at high-risk versus low-risk of dyslexia before they are taught to read. Atypical sensory and executive processing may then reduce the benefits that at-risk children receive from tuition in reading. Their sensory difficulties make learning to read more effortful, despite adequate tuition. They fall behind, become discouraged and read even less. Accordingly, there is atypical development of the left-lateralized ‘reading network’, as indeed found by Clark et al. in the structural scans taken at the age of 11 years.

Importantly, Clark et al. studied the development of cortical thickness within each participant as the children learned to read. As the low-risk group developed reading expertise, there was significant thickening of some areas of cortex, and thinning of others (notably lingual gyrus). Meanwhile, by the third scan at age 11, these areas had either also thickened in the dyslexic group (frontal and cingulate cortex), so that group differences were no longer significant, or had remained constant (lingual gyrus), also eliminating group differences. The only structure in which group differences were consistent over development was primary auditory cortex. Heschl’s gyrus was still significantly thinner in the children with dyslexia by the end of the study.
This finding is theoretically important. It suggests that auditory impairments are primary in the aetiology of developmental dyslexia. Indeed, it is notable that the few other longitudinal research studies of dyslexia utilizing neuroimaging and beginning prior to schooling have also identified atypical auditory processing as characterizing the at-risk samples (e.g. Raschle et al., 2011). Two of these studies (in Finnish and Dutch) began in infancy, and both identified a range of neonate and infant auditory weaknesses using EEG (for example, in syllable discrimination, pitch discrimination and vowel duration discrimination; Guttorm et al., 2010; Van Zuijen et al., 2013). These auditory weaknesses predicted later phonological awareness and reading ability in the two languages.

Neuroimaging demonstrations of structural and functional neural differences nevertheless leave open the question of mechanism. Here, the auditory neuroscience of speech processing may offer some insights. In multi-time resolution models of speech processing, endogenous oscillatory activity in the auditory cortex becomes rhythmically-entrained to amplitude modulation patterns in the speech signal at different temporal rates, thereby encoding speech information at multiple timescales (Giraud and Poeppel, 2012). Recent studies in dyslexia have revealed impaired delta band entrainment (~0.5–4 Hz) to slower amplitude modulations in the dyslexic brain. Adult dyslexics showed impaired neuronal entrainment to amplitude modulations at 2 Hz, with group differences localized to sources close to Heschl’s gyrus (Fig. 1). Children with dyslexia showed atypical delta phase alignment to a rhythmic speech stream (‘ba…ba…ba…’), entraining to less informative points of the speech signal (Power et al., 2013).

Slow amplitude modulations around 2 Hz encode patterns of syllable stress (prosodic patterns). When a syllable is stressed, the amplitude ‘rise time’ (to the modulation peak) is larger. Amplitude modulation rise times appear to reset ongoing neuronal oscillations to achieve phase alignment, and children with dyslexia in a number of languages (English, French, Spanish, Chinese, Finnish, Dutch and Hungarian) show rise time impairments (Goswami, 2011). Poor rise time discrimination would affect oscillatory phase alignment. This in turn would affect the perceptual organization of amplitude modulations into linguistic units, causing prosodic and syllable-level impairments across languages. These ‘large grain size’ impairments would have consequences for phonological awareness of smaller units like phonemes (Goswami, 2014).

To date, there are no longitudinal studies of at-risk samples beginning in infancy that have studied rise time discrimination or oscillatory entrainment. However, we have recently begun such a study, and have found an interesting phenomenon in maternal speech that supports the developmental importance of entrainment to 2 Hz amplitude modulations (Leong et al., 2014). Australian-English speaking mothers using infant-directed speech showed a ‘stress shift’ when speaking to their babies (infant-directed speech measured at 7, 9, 11, 15 and 19 months). There was a selective shift toward rhythmic synchronization of amplitude modulations at slower temporal rates (stress rate-syllable rate; 2 Hz–5 Hz) when speaking to the younger babies. The ‘stress-shift’ observed would elicit stronger delta (~2 Hz) entrained oscillatory activity. Therefore, if infants at family risk for dyslexia turn out to show auditory entrainment impairments at the delta rate, this neural mechanism could be related to the structural differences reported in Clark et al.’s study.

Notably, Clark and colleagues reported no differences in phonological awareness between their high-risk and low-risk children prior to literacy instruction. Importantly, they measured phonemic awareness, which emerges largely as a consequence of tuition in reading. The strong prediction from the delta entrainment acoustic hypothesis outlined here would be that differences in prosodic and syllabic awareness would be most marked in pre-reading at-risk samples. Prosodic difficulties have not yet been widely studied in dyslexia. Potential visual difficulties in pre-reading at-risk samples are also seldom studied (Goswami, 2014). Yet as Clark et al. observe, the developmental patterns found for lingual gyrus may indicate reduced capacity for experience-dependent plasticity in visual cortex. There is modest support for this from a second Dutch longitudinal study of at-risk pre-readers, which found pre-school differences in visual processing (Boets et al., 2011). However, these visual processing differences were not sustained after reading tuition commenced, which also fits Clark et al.’s findings.

More longitudinal cohort studies are clearly required to establish the neural basis of dyslexia, including a wider range of neurocognitive measures (auditory, visual and executive function). While such studies are the most challenging to deliver, requiring long-term commitment from families, funders and researchers, they are also the only experimental design capable of providing unambiguous information about causality.
In quest of the oscillator(s) in tremor: are we getting closer?

This scientific commentary refers to ‘The nature of tremor circuits in parkinsonian and essential tremor’ by Cagnan et al. (10.1093/brain/awu250).

Periodic oscillatory activity is abundant in the nervous system (Gray, 1994), both in health and in disease. Ion channels, membrane potentials, action potentials of single neurons and microscopic brain regions all show periodic oscillations (hereafter ‘oscillations’). Within this framework, the neuronal oscillators that generate tremor, an oscillatory phenomenon in its own right, are being sought. However, attempts to define the neuronal substrate/s that generate rest and postural tremors in Parkinson’s disease and essential tremor face a number of conceptual difficulties. Correlation does not imply causality, thus strong coherence between tremor and neuronal oscillations could be the result of peripheral feedback to the nervous system. Many researchers have therefore focused on active manipulation of tremor phenomena. However, the ability to attenuate or modulate tremor by stimulating a certain brain structure does not necessarily prove that this locus is the tremor generator. What features can be used to distinguish between the tremor generator and the downstream neuronal pathways that transmit the oscillatory signal? In this issue of Brain, Cagnan et al. (2014) address this question and others by testing the effect of electric stimulation on tremor in patients who underwent deep brain stimulation (DBS) surgery.

Cagnan et al. compared three group of patients—individuals with Parkinson’s disease and chronically implanted electrodes in either the subthalamic nucleus (n = 7) or the ventrolateral thalamus (n = 8), and patients with essential tremor and electrodes in the ventrolateral thalamus (n = 10). Stimulation was applied for each individual at a frequency that was close to, but not identical to, that of the patient’s own tremor. Small differences between the frequencies of tremor and stimulation unlocked these two oscillatory processes. Therefore, in each tremor cycle, stimulation was applied at a slightly different phase. This enabled the researchers to test stimulation-induced phase locking and the effects on tremor amplitude of stimulation in different phases.

Recording limb tremor with accelerometers revealed stimulus-induced entrainment of tremor in all three groups, even though strong phase-locking was not observed. The tremor frequency per se did not change. While entrainment did not distinguish Parkinson’s disease from essential tremor, the precise timing of stimulation relative to the phase of tremor did separate these two diseases. In essential tremor, the stimulus modulated the amplitude of tremor differently when applied in different phases of the tremor cycle. This phase-dependent modulation was not observed in Parkinson’s disease, whether the ventrolateral thalamus or the subthalamic nucleus was stimulated.

Cagnan and colleagues’ work may be approached in the context of previous studies that have used phase resetting to look for tremor generators. In phase resetting a perturbation that is delivered to an oscillatory system changes the timing of the following cycles (Fig. 1). It has generally been assumed that only perturbations applied to the oscillator itself, and not to other downstream