Towards the elucidation of the genetic and brain bases of developmental speech and language disorders

Two papers in this issue of *Brain* by Watkins and colleagues (Watkins *et al.*, 2002a, b) provide fascinating and important new data about the core behavioural features and neural basis of an inherited form of speech and language disorder. This work is particularly relevant in the light of recent discoveries about the genetic basis of the same developmental disorder.

Individuals affected by developmental speech and language disorders have major difficulties acquiring expressive and/or receptive language despite adequate intelligence and opportunity, and in the absence of any profound sensory or neurological impairment (Bishop *et al.*, 1995). Although twin studies consistently show a significant genetic component, the majority of families show a complex pattern of inheritance. The present studies concern the unique three-generation pedigree, the KE family, in whom a severe speech and language disorder is transmitted as an autosomal-dominant monogenetic trait. Speech in affected individuals is effortful, distorted and often unintelligible with word order and other grammatical errors. Previous work on the KE family had mapped the locus responsible (SPCH1) to 7q31 (Fisher *et al.*, 1998). Further studies by the same research group have now identified a point mutation in affected family members, which alters an invariant amino acid residue in the DNA-binding domain in a forkhead/winged helix transcription factor, encoded by the FOXP2 gene (Lai *et al.*, 2001). The case for a causal association is further strengthened by the finding of a translocation break in the same gene in another unrelated individual who has a very similar speech and language disorder (Lai *et al.*, 2001). Many members of the forkhead/winged helix protein family are known to be regulators of embryogenesis and mutations of the FOX genes have been implicated in a range of other human developmental disorders. Lai *et al.* (2001) propose that an insufficient dosage of critical forkhead transcription factors during embryogenesis, leads to maldevelopment of brain speech and language regions of the brain.

Developing a full understanding of neural basis and associated cognitive/linguistic deficits in the KE family is clearly important particularly with the hope of future gene based therapies.

In their first paper, Watkins *et al.* (2002a) describe the results of detailed volumetric measurements, using the automated technique of voxel-based morphometry (VBM) supplemented by targeted manual volumetry, in affected and unaffected members of the KE family, and a group of age-matched controls. In contrast to simple visual inspection of MRIs, the sophisticated methods employed by the authors demonstrated clear abnormalities in the affected family members that were not present in behaviourally normal members of the family. The direction of the difference was not, however, a simple matter of reduced cortical volumes, as some regions were larger than normal; while the caudate nucleus and inferior frontal gyrus were found to be reduced in size bilaterally, the left frontal opercular region (pars triangularis and anterior insular cortex) and the putamen bilaterally had a greater volume of grey matter. It is tempting to simplify the finding of studies using volumetric analyses to a ‘big is better’ paradigm. We have been guilty of adopting this approach ourselves (Harasty *et al.*, 1997, 2001; Galton *et al.*, 2001), although this assumption is probably more valid in acquired degenerative brain disorders. Recent data have shown that in some instances, such as stuttering, bigger is certainly worse. For instance, Foundas *et al.* (2001) showed that stutterers have an increase in cortical volume in two main speech areas. Ongoing work in one of our laboratories (J. A. Harasty *et al.*, unpublished observations) has replicated this finding in stutterers but has found, in addition, that white matter tracts underlying the abnormally large cortical regions are reduced, suggesting that corticocortical connections have failed to develop normally. Similar findings have been reported in some areas of the brain of dyslexic individuals but often involving the right hemisphere and implicating, therefore, a defect in the development of normal brain asymmetry (Galaburda *et al.*, 1985).

One possible explanation for a bigger cortex in developmental disorders is a lack of apoptosis (or programmed cell death) that occurs in the normal developing brain. Such cellular pruning presumably enhances the cortex’s specialization and ensures that appropriate cellular connections occur (Seldon, 1981). Perhaps a larger cortical gyral volume in certain brain regions suggests that this important developmental process did not occur leaving a more haphazard cellular structure whose lack of form and structure impede cortical functioning.

The results of the study by Watkins *et al.* (2002a) highlights the importance of subcortical structures particu-
larly the caudate nucleus and putamen in language development. Interestingly, the dorsal part of the caudate appeared to be particularly involved in the KE family, a pattern of volume loss similar to that found in Huntington’s disease (Vonsattel et al., 1985). Furthermore, the volume of the caudate nucleus was significantly correlated with the performance of affected family members on tests of oral praxis and nonword repetition but with a complex pattern: the greater the reduction on the left, the poorer the performance on a test of oral praxis, whereas the greater the reduction on the right, the better the performance on a test of nonword repetition requiring complex articulation. The authors are wisely cautious in their interpretation of this pattern given the relatively small number of subjects involved. One final comment relates to the bilateral nature of the abnormalities which point to a very generalized defect in neural development and tie in with the finding of their parallel behavioural study discussed below.

The companion paper by Watkins et al. (2002b) explores, in some detail, the behavioural consequences of the gene mutation and resultant neural maldevelopment. Thirteen affected and 12 unaffected members of the KE family were assessed using a comprehensive battery of tests of general intellectual ability, receptive and expressive language and praxis. Exactly the same battery was also given to a group of 11 patients with aphasia resulting from left hemisphere strokes which involved the opercular region. The findings provide an important contrast to other studies of individuals with developmental speech and language problems. Tallal and colleagues have argued persuasively in favour of a core defect in temporal processing of speech sounds, and moreover that specific temporal order re-training can ameliorate the problem (Tallal et al., 1983). Gathercole and Baddeley (1990) have proposed that a deficit in the phonological loop component of working memory represents the key defect in some cases. Others, such as Rice and Wexler (1986) have suggested that a deficit in the development of the grammatical aspects of language characterises specific developmental speech and language disorders. Even the nature of the disorder in the KE family has been the topic of considerable debate among different groups of investigators. The first report of the KE family described affected members as suffering from a ‘severe form of developmental verbal apraxia’ (Hurst et al., 1990). Gopnik and colleagues have focused on the linguistic impairments in affected individuals; in particular, their deficit in the use of infectious morphosyntactic rules (e.g. changing word endings to mark tense and number), which has been described as selective (Gopnik and Goad, 1997).

One major finding of the Watkins et al. (2002b) study is that affected members of the KE family have widespread deficits which involve virtually all aspects of speech and language, as well as aspects of non-verbal intelligence. Indeed, affected members and patients with stroke-related aphasia had remarkably similar profiles of impairment on the tests administered, except that the aphasia group had less impairment on non-verbal tasks. Longitudinal test scores available in a subset of younger affected individuals showed a progressive decline in performance IQ. These findings suggest that ‘a developmental speech and language disorder could have detrimental effects on various components of nonverbal intelligence, as well as lexical development and familiarity with the articulation of common word’. The finding of the present study also make untenable the prior claims that the family has a specific deficit in morphosyntactic rule usage. Watkins et al. (2002b) argue, instead, in favour of a core deficit in sequencing and learning of verbal and nonverbal associations, although the exact nature of this core deficit requires clarification. From a practical viewpoint, affected and unaffected family members were best discriminated on a test of nonword repetition thus confirming the value of this simple test in screening for developmental speech and language impairment (Gathercole and Baddeley, 1990; Bishop et al., 1996). Whereas Gathercole and Baddeley, who devised the test, have suggested that impairment in nonword repetition is related to a specific deficit in the storage of phonological information in working memory, the present authors propose that the defect in the KE family reflects deficits not in phonological memory per se, but rather in sequential articulation of phonological units. It remains possible, if less parsimonious and attractive, that the FOXP2 gene defect produces multiple independant speech, language and cognitive impairments. It should also be remembered that the study involved members of a single, and in many ways, unique kindred and may be applicable to other individuals with development speech and language disorders. As with other clinical neuropsychological syndromes, it is highly likely that this represents a heterogeneous disorder which has a number of different underlying cognitive explanations.

As well as the specific implications, these landmark studies illustrate the importance of a combined multi-disciplinary approach. These two papers represent a triumph for international collaboration and dogged determination on the part of the scientists and clinicians involved to pursue both the cause and the wider implications of this fascinating disorder. It is through the combination of genetic, neuroanatomical and cognitive analyses of this type that further advances are likely to be made in this and other developmental and degenerative disorders of the nervous system.

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References


