Alterations in structural connectivity may contribute both to the occurrence of tics in Gilles de la Tourette syndrome and to their subsequent control

This scientific commentary refers to ‘Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome’ by Worbe et al. (doi:10.1093/brain/awu311).

Tourette syndrome is a developmental disorder of childhood onset characterized by the presence of involuntary, recurring movements and utterances known as tics. It is more prevalent in boys than in girls (~4:1) and typically follows a developmental time course in which, in the majority of individuals, tics are either absent or mild by early adulthood. Adults with Tourette syndrome can thus be viewed as unrepresentative of the more general Tourette population (i.e. children and adolescents with the disorder), but nevertheless constitute an important group in which the clinical phenotype is stable and the compensatory plastic changes thought to bring about increased control over tic severity during adolescence (Jackson et al., 2011) have either failed to occur or have been ineffective.

While the neurobiology of Tourette syndrome is unclear, it is thought to involve disinhibition of cortico-striato-thalamo-cortical (CSTC) circuits, which are a connected set of brain structures involved in the planning and execution of movements (Albin and Mink, 2006) and in the formation of habits (Graybiel, 2008). The responsiveness of neurons in the striatum depends upon the salience of perceived stimuli, which can either be rewarding or aversive (Blazquez et al., 2002), and repeated exposure to the same salient stimuli is thought to result in a particular response being reinforced to produce a habit. It is hypothesized that in Tourette syndrome this habit formation process is over-extended (Graybiel, 2008) with neurons in the striatum becoming active in inappropriate contexts leading to disinhibition within thalamic and cortical target regions and resulting in unwanted actions becoming reinforced as tics (Albin and Mink, 2006). In a new paper published in Brain Worbe et al. (2014) add to our understanding of this process by examining alterations in connectivity within the CSTC pathways in adults with Tourette syndrome.

During the last decade a number of imaging studies have investigated abnormalities in the brain structure of individuals with Tourette syndrome. However, the results from these studies have been mixed, with many inconsistent or seemingly contradictory findings reported (Thomalla et al., 2009; Jackson et al., 2011; Cheng et al., 2014). Several factors are likely to contribute to these mixed results. For instance, previous studies have often drawn conclusions based upon samples with quite different characteristics. These include the presence of co-morbid disorders, differences in medication, and most importantly differences in age. Furthermore, many previous studies have failed to distinguish between alterations in structural connectivity that may be seen as primary causes of Tourette syndrome, and those that should be considered as secondary consequences, associated with compensatory or adaptive changes that aid in the control of clinical symptoms.
One finding that has consistently emerged from studies in children and adolescents with Tourette syndrome is that alterations in the microstructure of white matter pathways projecting to sensorimotor regions of cortex, such as reduced white matter connectivity in the corpus callosum (Plessen et al., 2006) or reduced fractional anisotropy (a measure of white matter microstructure) again in the corpus callosum (Jackson et al., 2011; Draper et al., 2014), are paradoxically associated with reductions in tic severity. These results have most often been interpreted as evidence for compensatory alterations in brain structure that aid in the control of clinical symptoms. By contrast, studies of adults with Tourette syndrome have reported a different pattern of results. Thomalla et al. (2009) described widespread increases in fractional anisotropy values in white matter pathways projecting to primary sensory and motor cortex in adults with the disorder and demonstrated that fractional anisotropy values in these pathways were negatively associated with tic severity. Similarly, Cheng et al. (2014) reported a negative association between white matter integrity and tic severity in pathways that connect the striatum to the supplementary motor area, but they also demonstrated reduced CSTC connectivity in their group of adults with Tourette syndrome.

The study by Worbe et al. (2014) provides important new information on this issue. Worbe and colleagues use high-resolution diffusion tensor imaging, together with probabilistic tractography techniques, to examine the connectivity of white matter tracts in a large sample of 49 adults with Tourette syndrome, and a group of individuals without neurological disorders and of comparable age. In the group with Tourette syndrome, there was enhanced structural connectivity in the white matter tracts linking the striatum and thalamus with cortical structures, including primary motor cortex, primary somatosensory cortex, and supplementary motor area. Importantly, consistent with the previous structural neuroimaging studies of adolescents with Tourette syndrome, this enhanced connectivity of the motor cortex was positively associated with increased motor tic severity.

One final intriguing aspect of the study reported by Worbe et al. relates to the gender composition of their sample of adults with Tourette syndrome. As noted above, in child and adolescent samples the ratio of boys to girls is typically ~4:1, but in the study by Worbe and colleagues, the ratio of females to males is closer to parity. This observation is consistent with the recent suggestion that the childhood gender bias for boys is attenuated in adulthood (Lichter and Finnegan, 2014). This may indicate that females with Tourette syndrome are less likely to undergo remission of tics during adolescence. It has been proposed that females may experience greater functional interference from tics than males (Lichter and Finnegan, 2014). Consistent with this proposal, Worbe et al. report the novel finding that females with Tourette syndrome have increased connectivity in CSTC pathways compared to males, which may contribute to increased tic severity.

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doi:10.1093/brain/awu338

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