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Towards a primate model of Gilles de la Tourette syndrome: Anatomo-behavioural correlation of disorders induced by striatal dysfunction

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ABSTRACT

Introduction: Gilles de la Tourette syndrome (GTS) is characterized by abnormal movements (tics) often associated with behavioural disorders. Neuropathological data from GTS patients have suggested that aberrant activation of distinct striatal functional territories could produce a large spectrum of GTS symptoms. In a monkey model, injections of GABA-antagonist into the striatum enabled us to produce tic-like movements, hyperactivity and stereotyped behaviours. These effects had similarities with simple motor tics, hyperactivity and compulsive behaviours observed in GTS patients. In this study, we first aimed to identify the neuronal circuits involved in the different behavioural effects using anatomical antero/retrograde tracer in monkeys. We also compared the neuronal circuits thus obtained with the available neuro-anatomical data on GTS patients.

Methods: Using injections of axonal tracer into different functional parts of the striatum of eight monkeys, we identified cortical, thalamic and basal ganglia regions related to the expression of tic-like movements, hyperactivity and stereotyped behaviours induced in response to micro-injection of GABA-antagonist.

Results: In this monkey model, different anatomical circuits involving distinct cortical and thalamic areas and sub-territories of the basal ganglia underpinned movement and behavioural disorders. Thus, tic-like movements were associated with neuronal labelling within the sensorimotor network, mostly in the medial and lateral premotor cortex and sensorimotor parts of the basal ganglia. Neuronal labelling in the prefrontal dorso-lateral cortex and associative territories of the basal ganglia was related to hyperactivity disorder and stereotyped behaviours were linked to the orbitofrontal cortex and limbic part of the basal ganglia.

Conclusions: These results support the hypothesis that different behavioural effects could arise from distinct but inter-digitated neuronal circuits. As these behavioural disorders shared some similarities with simple motor tics, hyperactivity and compulsive behaviours observed in GTS patients, this model could be a good tool for future studies involving the modulation of neuronal circuits, such as deep brain stimulation.

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1. Introduction

Gilles de la Tourette syndrome (GTS) is a neurodevelopmental disorder characterized by simple and complex motor and vocal tics. Simple tics are brief, recurrent and non-rhythmic motor or vocal productions, such as eye blinks or throat noise. Complex tics are complex motor or vocal actions displaced from normal context, like touching behaviour or repetitive word pronunciation (Jankovic and Fahn, 1986). In GTS, the tics are often associated with such behavioural disorders as attention-deficit with hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD) (Cavanna et al., 2009).

It has been suggested that dysfunction of different cortico-basal ganglia circuits could account for the heterogeneous clinical expression of GTS (Mink, 2006). This hypothesis is based on the functional division of cortico-basal ganglia circuits into sensorimotor, associative and limbic circuits, which are respectively implicated in motor, cognitive and motivational aspects of behaviour (Alexander et al., 1986).

Numerous neuroimaging studies on GTS patients have corroborated this hypothesis. Thus, simple tics were shown to be associated with structural and functional abnormalities in sensorimotor networks and mostly in the premotor and motor cortices (Sowell et al., 2008; Bohlhalter et al., 2006; Worbe et al., 2010), in white matter of the cortico-spinal tract and in the posterior thalamus (Thomalla et al., 2009).

In contrast to simple tics, complex tics were found to be associated with structural abnormalities in prefrontal and parietal cortical areas (Worbe et al., 2010), which are part of the associative functional circuit.

Finally, the presence of psychiatric co-morbidities, such as OCD and ADHD, is reported to be correlated with structural and functional abnormalities in limbic structures, such as the ventro-medial prefrontal cortex (Worbe et al., 2010), the anterior putamen and caudate nucleus (Bloch et al., 2005; Peterson et al., 2003; Radua et al., 2010), the ventral striatum (Draganski et al., 2010), the amygdala and the hippocampus (Peterson et al., 2007). Furthermore, structural changes in the anterior striatum, including both putamen and caudate, were also found in ADHD (Nakao et al., 2011) and OCD (Radua et al., 2010) patients without tics.

The precise mechanism of the dysfunction of cortico-basal ganglia networks in GTS is poorly understood. Nonetheless, impaired inhibition of striatal projection neurons has been suggested as a primary pathophysiological mechanism of tics and related behavioural disorders (Mink, 2003). This hypothesis is supported by the results of post-mortem analyses of basal ganglia tissue, which identified the deviant distribution and structure of gamma amino butyric acid (GABA) inhibitory neurons in GTS patients (Kalanithi et al., 2005; Kataoka et al., 2010).

A monkey model of simple motor tics (McCairn et al., 2009; Worbe et al., 2009) and behavioural disorders including hyperactivity and complex stereotyped actions was proposed involving pharmacological manipulation of GABA-ergic inhibition within the different sub-territories of the globus pallidus (GP) (Grabli et al., 2004) and the striatum (Worbe et al., 2009). Thus, this primate model suggests that movement and behavioural disorders could arise from a similar pathophysiological mechanism. This model also provides an opportunity to determine precisely the site where local neuronal disinhibition produces behavioural effects and to describe the specific neuronal circuits underlying these effects. Clearly, any comparison between the behavioural effects obtained in the monkey model and the clinical presentation in patients should be considered with caution. Nonetheless, this model could be a useful tool for guiding neuromodulation techniques such as deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation. Indeed, using DBS of the subthalamic nucleus, we were able to show a reduction of the stereotyped behaviours obtained following bicuculline microinjections into the limbic territory of the external segment of the GP (Baup et al., 2008). These results are consistent with data on DBS in OCD patients, since the subthalamic nucleus is reported to be a suitable target for the surgical treatment of OCD (Mallet et al., 2008).

In this study we aimed first to determine the afferent and efferent connections of the neurons located in the different sites of the striatum where microinjections of GABA-antagonist bicuculline induced simple tic-like movements, hyperactivity state and stereotyped behaviours. To this end, injections of axonal antero-retrograde tracer were performed in the striatal sites where the most characteristic movement and behavioural effects had been obtained in monkeys.

We also compared the neuronal circuits identified in our monkey model with the known neuroanatomy of tics and behavioural disorders in GTS patients.

2. Materials and methods

2.1. *Subjects*

Seven adult male macaque monkeys (six *Macaca fascicularis* MI 59, MI 60, MI 65, MI 66, MI 69, MI 70, one *Macaca mulatta* MM 37) and one male African green monkey (*Cercopithecus aethiops sabaeus*, CA 34) were used in this study. The behavioural data obtained in one monkey (MM 60) were previously reported in the study on the effects of bicuculline microinjections in the striatum (Worbe et al., 2009).

All monkeys weighed between 4 and 6 kg and were aged between 3 and 5 years. All studies were carried out in accordance with European Communities Council Directive of 1986 (86/609/EEC). The animals were kept under standard conditions (12-h light/dark cycle, 23 °C and 50% humidity).

2.2. *Microinjections of bicuculline and behavioural analysis*

Three types of bicuculline effects that are similar to the expression of GTS symptoms were searched for using the injection of anatomical tracer: tic-like movements, hyperactivity state associated with touching behaviour and stereotyped behaviours characterized by an increase of grooming and licking or biting fingers.

A detailed description of the behavioural effects and the schedule of experimental sessions are provided in a previous study (Worbe et al., 2009). Briefly, the coordinates of the

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