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Diversity and complexity in the pyramidal tract projectome

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In their response to my Review (Corticostriatal connectivity and its role in disease. *Nature Rev. Neurosci.* **14**, 278–291 (2013))[1], Smith *et al.* (Corticostriatal and mesocortical dopamine systems: do species differences matter? *Nature Rev. Neurosci.* http://dx.doi.org/10.1038/nrn3469-c1 (2013))[2] highlight fascinating topics and present intriguing new ideas and schematics, which I hope will help to stimulate more research and discussion in these important areas. In this limited space, I focus on the pyramidal tract (PT)-related issues. For primate-related intratelencephalic (IT) versus PT issues, readers are referred to Pasquereau and Turner's pivotal study[3], and terminological clarifications may be sought in my Review and references therein[1].

The PT system follows a basic mammalian plan, with many evolutionary specializations[4–9]. Smith *et al.*[2] propose a distinction in which the supraspinal branching of single PT axons is extensive in rats but mostly absent in primates. Undoubtedly, PT branching is somehow differentiated across mammals, and the proposed organization may be correct. As touched on below, I wonder whether aspects of this proposal may be considered tentative, but certainly the new formulation offers well-defined starting points for further investigation.

Additional considerations include the following. One is the paucity of data; much hinges on the 10 primate and 25 rat PT axons described in two key studies[10,11] (for comparison, a human PT contains ~10^6 axons[12]). A methodological concern is under-detection of axonal branching (which is discussed in REF. 10), a problem that is presumably amplified in larger-brained animals, resulting in greater apparent sparseness of branching. The anatomical arrangement in rats that has been proposed by Smith *et al.*[2] is similar to figure 1a of my article[1]. However, that schematic represents the overall macroscopic (not single-axon) organization of the mammalian PT projection[4,9] (note that 'PT' refers broadly to corticofugal neurons with subcerebral projections, such as corticospinal, corticobulbar, and so on[1,9]). The reconstruction of a rat PT neuron shown in the figure 1c of REF. 1 (originally in REF. 11) was included to illustrate the actual complexity at the single-axon level. The crucial points in the present context are that, first, single PT axons in the rat typically innervate many — but not all — potential targets, and, second, they do so in diverse combinations. For example, many axons with subthalamic nucleus (STN) branches lack striatal branches[11]. Other rat data suggest even sparser PT branching[13]. In mice, there is still little known about PT axons' branching patterns. In monkeys, single PT axons can innervate either, neither, or both the STN and midbrain[10], and can branch to brainstem centres[14] (claustral branches, however, come from IT axons[10]). In cats, single PT axons similarly innervate various targets in diverse combinations[15,16]. Thus, the available data across species indicate substantial axon-to-axon variability in PT branching and suggest that arborization patterns tend to fall somewhere between the all-or-none extremes depicted in the new schematics.

"We have to over-simplify in order to experiment at all, but must never allow ourselves to forget the very real complexity of our living material" (REF. 4) — and fittingly enough, Phillips and Porter, pioneers in research on motor cortex and PT neurons, were discussing PT projections. Making sense of the diversity and complexity of PT projections is an ongoing challenge. Schematics have vital roles in this endeavour as usefully over-simplified working models to guide the pursuit of more data, which remains a top priority. Indeed, it still holds that: "Much combined microscopical and electroanatomical work will be needed before we have the complete catalogue of the PT collaterals" (REF. 4).

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doi:10.1038/nrn3469-c2
Published online 4 December 2013

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Acknowledgements
G.M.G.S. has received funding from US National Institutes of Health-National Institute of Neurological Disorders and Stroke grant NS061963 and the Whitehall Foundation.