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LETTER TO THE EDITOR

Cognition in SCA21 reflects developmental and adult onset cerebellar cognitive affective syndrome

Pedro Braga-Neto,[1,2] José Luiz Pedroso,[2] Orlando G. P. Barsottini[2] and Jeremy D. Schmahmann[3]

1 Center of Health Sciences, Universidade Estadual do Ceará, Fortaleza, Ceará, Brazil
2 Department of Neurology, Ataxia Unit, Universidade Federal de São Paulo, São Paulo, Brazil
3 Ataxia Unit, Cognitive Behavioural Neurology Unit, Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston MA 02114, USA

Correspondence to: Pedro Braga-Neto, MD, PhD.,
Center of Health Sciences, Av. Dr. Silas Munguba, 1700, Campus do Itaperi, 60.714-903,
Universidade Estadual do Ceará
E-mail: pbraganeto@gmail.com.

Correspondence may also be addressed to: Jeremy D. Schmahmann, M.D. Department of Neurology, Massachusetts General Hospital, Suite 340, Charles River Plaza South, 175 Cambridge Street, Boston, MA 02114 E-mail: jschmahmann@partners.org

Sir,

We read with interest the article by Delplanque *et al.* (2014) entitled: 'TMEM240 mutations cause spinocerebellar ataxia type 21 with mental retardation and severe cognitive impairment'. The striking feature of the clinical presentation was not only the cerebellar ataxia and cerebellar volume loss on imaging, but also the cognitive and neurobehavioural impairments that were pervasive, and—in the younger onset cases—severe enough to warrant the designation of severe mental retardation. The neuropsychological examinations of the SCA21 kindreds disclosed moderate impairments in attention, executive function, short-term, working and episodic memory abilities and, marked impairments in action planning, abstract reasoning, language and visuospatial functions. The authors also report neuropsychiatric phenomena including impulsivity, aggression and apathy etc.

Despite the centrality of the cognitive and neurobehavioural features in this report of the genetic basis and clinical manifestations of SCA21, the authors do not reflect on the importance of their observations for our understanding of the wider role of the cerebellum beyond motor control, of which this case series represents a prime example.

A framework now exists within which cognitive impairments in widespread cerebellar neurodegenerative disorders may be understood. The cerebellar cognitive affective syndrome (CCAS; Schmahmann and Sherman, 1998) is characterized by impairments in executive, visuospatial and linguistic functions as well as changes in affect. The emotional and behavioural symptoms that characterize the affective changes were further defined within the domains of attentional control, emotional control, autism spectrum, psychosis spectrum, and social skill set (Schmahmann *et al.*, 2007). These neurobehavioural phenomena are viewed as manifestations of dysmetria of thought, loss of the universal cerebellar transform applied not only to sensorimotor processing, but also to intellectual function, emotion and autonomic control (Schmahmann, 1991, 2010). Further, the relatively greater impact on cognitive and emotional development in the early onset cases is thought to reflect the loss of sustaining connections between cerebellum and associative and paralimbic regions of the cerebral cortex that are essential for normal development. In the absence of obvious pathology in cerebral cortical and subcortical regions, and in the presence of the primary anatomical locus of pathology in the cerebellum in SCA21, it is reasonable to consider that the bulk of the cognitive deficits in this disorder are consistent with developmental or adult onset CCAS.

A wide range of cognitive deficits are now recognized in patients with spinocerebellar ataxias and other hereditary ataxias, including impairments in executive function, visual

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Table 1 Summary of studies on cognitive deficits in hereditary ataxias, highlighting the main neuropsychological findings

Study	Hereditary ataxia	Patients (*n*)	Cognitive deficits
Radvany *et al.*, 1993	SCA3	35	Visual memory, visuospatial processing, colour discrimination
Maruff *et al.*, 1996	SCA3	6	Visual attention
Zawacki *et al.*, 2002	SCA3	6	Executive function
Bürk *et al.*, 2003	SCA1, 2 and 3	36	Verbal memory and executive deficits
Kawai *et al.*, 2004	SCA3	16	Verbal and visual memory, verbal fluency, visuospatial and constructional
Klinke *et al.*, 2010	SCA1, 2, 3 and 6	36	Frontal-attention and executive dysfunction
Tedesco *et al.*, 2011	SCA1, SCA2, FRDA, AT and DVE	24	Language, visuospatial abilities, executive function, sequencing abilities and visuospatial memory
Braga-Neto *et al.*, 2012	SCA3	38	Executive and visuospatial functions
Verhoeven *et al.*, 2012	ARSACS	2	Executive and motivation impairment
Nieto *et al.*, 2012	FRDA	36	Executive, visuoconstrutive and visuoperceptive dysfunction and poor action naming
Roeske *et al.*, 2013	SCA3	11	Verbal learning, verbal and nonverbal memory
Lopes *et al.*, 2013	SCA3	32	Episodic and working memory
Fancellu *et al.*, 2013	SCA1 and 2	42	Executive functions and visuospatial and visuoperceptive function

SCA = spinocerebellar ataxia; ARSACS = autosomal recessive spastic ataxia of Charlevoix-Saguenay; FRDA = Friedreich's ataxia; AOA2 = ataxia with oculomotor apraxia type 2; AT = ataxia-telangiectasia; DVE = deficiency of vitamin E.

spatial performance, and selected aspects of memory (Radvany *et al.*, 1993; Maruff *et al.*, 1996; Zawacki *et al.*, 2002; Bürk *et al.*, 2003; Kawai *et al.*, 2004; Klinke *et al.*, 2010; Tedesco *et al.*, 2011; Braga-Neto *et al.*, 2012; Verhoeven *et al.*, 2012; Fancellu *et al.*, 2013; Lopes *et al.*, 2013; Roeske *et al.*, 2013) (Table 1), although circumspection is warranted. In the absence of neuropathological examination of the nervous system of individuals with SCA21 and cognitive/neuropsychiatric manifestations, it is still possible that higher order deficits may result from degeneration of focal cortical areas or of subcortical structures (thalamus, caudate nucleus, hippocampus) in addition to disruption of the cerebrocerebellar loops impaired by the cerebellar degeneration (Pedroso *et al.*, 2013; Braga-Neto *et al.*, 2014). However, the authors provide no pathological counterpoint to the cerebellum-as-cause hypothesis, and there are no published reports of SCA21 neuropathology. Further, the brain imaging in this and previous reports (Vuillaume *et al.*, 2002) spares the brainstem, with only non-specific T_2 and FLAIR hyperintensities noted in periventricular white matter (ages of affected individuals not provided), with the brunt of pathology located in the cerebellum, including the vermis, previously implicated as the limbic cerebellum (Schmahmann, 2010).

Delplanque and colleagues add to our knowledge of the genetic and clinical characteristics of SCA21. But they also provide clinical data adding considerable weight to the recognition that dysmetria of movement, i.e. cerebellar ataxia, is merely one manifestation of the cerebellar clinical syndrome. Dysmetria of thought, manifesting as the CCAS (including the cognitive and neuropsychiatric disorders of cerebellar origin), is consistent with current notions of topographically arranged cerebellar linkage with non-motor areas of the cerebral cortex in animals (Schmahmann and Pandya, 1997; Strick *et al.*, 2009) and human (Buckner *et al.*, 2011), with task-based functional MRI studies of cerebellar activation by motor and non-motor tasks (Stoodley and Schmahmann, 2009), and with the clinical phenomenology resulting from lesions of the cerebellum (Schmahmann and Sherman, 1998; Braga-Neto *et al.*, 2012). Further study of the SCA21 families with functional brain imaging may be highly informative for our understanding of the pathophysiology of their cognitive and neurobehavioural impairments.

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