Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see <http://www.jneurosci.org/content/jneurosci-journal-club>.

Spinocerebellar Ataxia Type 6: A Disorder of Connectivity?

Max Teaford

Department of Psychology, Miami University, Oxford, Ohio 45056

Review of Yacoubi et al.

Spinocerebellar Ataxia Type 6 (SCA6) is a progressive neurodegenerative disorder that affects Purkinje cells in the cerebellum, particularly in the vermis and surrounding regions, including lobule VI (Panouillères et al., 2017). This disorder arises in adulthood (mean age of onset ~45 years) and is characterized by several behavioral, sensory, and motor impairments (Gierga et al., 2009; Casamento-Moran et al., 2015). One symptom, which is particularly noteworthy, is the inability to perform accurate movements (Yacoubi et al., 2020).

Previous work by Casamento-Moran et al. (2015) demonstrated that individuals with SCA6 exhibited fewer errors in timing muscle contractions and more errors in force (i.e., contracting muscles more than needed) than control participants, when performing a task where they had to bend their left ankle upward in a specified amount of time and with a specified amount of force. This finding was in stark contrast with studies involving other populations with cerebellar pathology, which found decreased precision of timing. In a recent study, Yacoubi et al. (2020) hypothesized that increased temporal precision in SCA6 results from lower temporal variability of movement. This hypothesis was based on previous research on

musicians, which found that reduced temporal variability is associated with a reduced volume of cerebellar lobule VI (a neuroanatomical region impacted by SCA6), thus suggesting that this may be a neural correlate of temporal invariance (i.e., less muscle contraction time variability) in individuals with SCA6 (Baer et al., 2015).

To determine whether individuals with SCA6 do indeed exhibit temporal invariance of movement, Yacoubi et al. (2020) had participants perform tasks involving ankle dorsiflexion (i.e., bending the ankle so the foot moved upward). First, participants performed a task to determine the maximal isometric contraction force they could achieve during voluntary ankle dorsiflexion. Then participants performed a goal-directed contraction task in which they attempted to match a target presented on a computer screen. To match the target, they had to perform isometric ankle dorsiflexion at 15% of their maximum voluntary force within 180 ms. After each trial, participants received feedback in the form of visual depictions of their muscle contraction relative to the target force and time. Finally, participants performed voluntary maximal isometric contractions of the ankle again (to rule out fatigue, although no analyses on these data were reported).

Relative to healthy control participants, individuals with SCA6 exhibited less temporal variability and made fewer timing errors, but they made more force errors (i.e., performed contractions at >15% of their maximum voluntary contraction force). In contrast, healthy control participants

and individuals with SCA6 did not differ with regard to force variability. These results support the authors' hypothesis that increased temporal precision of ankle dorsiflexion in people with SCA6 was associated with reduced temporal variability.

Next, the authors asked whether the behavioral effects were associated with changes in cerebellar volume as measured with MRI. The authors found that lower gray matter volume in cerebellar lobule VI was associated with temporal invariance. In addition, lower temporal variability was associated with disease severity, but not disease duration. Based on the results of this study, Yacoubi et al. (2020) suggest that the degeneration of cerebellar lobule VI may result in a reduced ability to modulate the duration of muscle contraction force. But in light of previous functional connectivity and postmortem studies on individuals with SCA6, several other neuroanatomical regions and processes likely contribute to temporal invariance. The following paragraph will elaborate on the functional anatomy and connectivity of cerebellar lobule VI to help underscore the importance of other neuroanatomical regions and processes that may play a role in the findings of Yacoubi et al. (2020).

Cerebellar lobule VI is located within the posterior cerebellum, which has somatotopic representations of the foot, hand, tongue, and eyes (Boillat et al., 2020). This lobule has been implicated in a plethora of functions, including timing of movements, sensorimotor adaptation, explicit motor sequence learning, encoding sensory prediction errors, and sensory attenuation

Received Apr. 8, 2020; revised Oct. 19, 2020; accepted Oct. 21, 2020.

I would like to thank Ingrid Teaford, Dr. L. James Smart, and Dr. Robin Thomas for feedback on drafts of this manuscript.

The author declare no competing financial interests.

Correspondence should be addressed to Max Teaford at teaforma@miamioh.edu.

<https://doi.org/10.1523/JNEUROSCI.0822-20.2020>

Copyright © 2020 the authors

(Donchin et al., 2012; Schlerf et al., 2012; Bernard and Seidler, 2013; Kilteni and Ehrsson, 2020). This region exhibits functional connectivity with several other neuroanatomical regions that are important in motor control, including the primary motor cortex (M1) and the supplementary motor area (SMA) (Kang et al., 2017). Interestingly, individuals with SCA6 have been found to exhibit degeneration of M1 as well as reduced functional connectivity between M1, SMA, and many cerebellar regions, including lobule VI (Gierga et al., 2009; Kang et al., 2017). This is noteworthy because previous studies with healthy individuals have demonstrated that activating M1 via transcranial magnetic stimulation results in increased temporal variability of movement and increased force control (Verstynen et al., 2006; Jin et al., 2019). Furthermore, repeated transcranial magnetic stimulation of the SMA impairs bimanual antiphase movements (Steyvers et al., 2003). Therefore, it seems likely that connectivity between cerebellar lobule VI and other neuroanatomical regions, particularly M1, plays a role in the findings of Yacoubi et al. (2020). Namely, decreased functional connectivity between M1 and cerebellar lobule VI may result in a reduced ability to fine tune the duration of muscle contractions before their execution.

Clearly more research is needed to investigate these possibilities. Studies using functional neuroimaging methods (e.g., fMRI) to examine whether differences in connectivity are predictive of single-joint

and multijoint movement task variability are recommended. Based on what is currently known, it is expected that connectivity between M1 and cerebellar lobule VI should be predictive of single-joint movement temporal variability. Whereas connectivity between the SMA and M1 should be predictive of spatial variability in multijoint task (assuming they require antiphase movements), such research could result in a more nuanced understanding of SCA6.

References

- Baer LH, Park MT, Bailey JA, Chakravarty MM, Li KZ, Penhune VB (2015) Regional cerebellar volumes are related to early musical training and finger tapping performance. *Neuroimage* 109:130–139.
- Bernard JA, Seidler RD (2013) Cerebellar contributions to visuomotor adaptation and motor sequence learning: an ALE meta-analysis. *Front Hum Neurosci* 7:27.
- Boillat Y, Bazin PL, van der Zwaag W (2020) Whole-body somatotopic maps in the cerebellum revealed with 7T fMRI. *Neuroimage* 211:116624.
- Casamento-Moran A, Chen YT, Kwon M, Snyder A, Subramony SH, Vaillancourt D, Christou EA (2015) Force dysmetria in spinocerebellar ataxia 6 correlates with functional capacity. *Front Hum Neurosci* 9:184.
- Donchin O, Rabe K, Diedrichsen J, Lally N, Schoch B, Gizewski ER, Timmann D (2012) Cerebellar regions involved in adaptation to force field and visuomotor perturbation. *J Neurophysiol* 107:134–147.
- Gierga K, Schelhaas HJ, Brunt ER, Seidel K, Scherzed W, Egensperger R, de Vos RA, den Dunnen W, Ippel PF, Petrasch-Parwez E, Deller T, Schöls L, Rüb U (2009) Spinocerebellar ataxia type 6 (SCA6): Neurodegeneration goes beyond the known brain predilection sites. *Neuropathol Appl Neurobiol* 35:515–527.
- Jin Y, Lee J, Oh S, Flores Gimenez CM, Yoon B (2019) Noninvasive brain stimulation over the m1 enhances bimanual force control ability: a randomized double-blind sham-controlled study. *J Mot Behav* 51:521–531.
- Kang N, Christou EA, Burciu RG, Chung JW, DeSimone JC, Ofori E, Ashizawa T, Subramony SH, Vaillancourt DE (2017) Sensory and motor cortex function contributes to symptom severity in spinocerebellar ataxia type 6. *Brain Struct Funct* 222:1039–1052.
- Kilteni K, Ehrsson HH (2020) Functional connectivity between the cerebellum and somatosensory areas implements the attenuation of self-generated touch. *J Neurosci* 40:894–906.
- Panouillères MT, Joundi RA, Benitez-Rivero S, Cheeran B, Butler CR, Németh AH, Miall RC, Jenkinson N (2017) Sensorimotor adaptation as a behavioural biomarker of early spinocerebellar ataxia type 6. *Sci Rep* 7:12.
- Schlerf J, Ivry RB, Diedrichsen J (2012) Encoding of sensory prediction errors in the human cerebellum. *J Neurosci* 32:4913–4922.
- Steyvers M, Etoh S, Sauner D, Levin O, Siebner HR, Swinnen SP, Rothwell JC (2003) High-frequency transcranial magnetic stimulation of the supplementary motor area reduces bimanual coupling during anti-phase but not in-phase movements. *Exp Brain Res* 151:309–317.
- Verstynen T, Konkle T, Ivry RB (2006) Two types of TMS-induced movement variability after stimulation of the primary motor cortex. *J Neurophysiol* 96:1018–1029.
- Yacoubi B, Casamento-Moran A, Burciu RG, Subramony SH, Vaillancourt DE, Christou EA (2020) Temporal invariance in SCA6 is related to smaller cerebellar lobule VI and greater disease severity. *J Neurosci* 40:1722–1731.