Citation for published version

Watson, T C and Koutsikou, Stella and Cerminara, N L and Flavell, C R and Crook, J J and Lumb, B M and Apps, R (2013) The olivo-cerebellar system and its relationship to survival circuits. Frontiers in Neural Circuits, 7. pp. 304-310.

DOI

Link to record in KAR

https://kar.kent.ac.uk/84444/

Document Version

Publisher pdf

Copyright & reuse
Content in the Kent Academic Repository is made available for research purposes. Unless otherwise stated all content is protected by copyright and in the absence of an open licence (e.g., Creative Commons), permissions for further reuse of content should be sought from the publisher, author or other copyright holder.

Versions of research
The version in the Kent Academic Repository may differ from the final published version. Users are advised to check http://kar.kent.ac.uk for the status of the paper. Users should always cite the published version of record.

Enquiries
For any further enquiries regarding the licence status of this document, please contact: researchsupport@kent.ac.uk

If you believe this document infringes copyright then please contact the KAR admin team with the take-down information provided at http://kar.kent.ac.uk/contact.html
The olivo-cerebellar system and its relationship to survival circuits

Thomas C. Watson1, Stella Koutsikou1, Nadia L. Ceminara1, Charlotte R. Flavell2, Jonathan J. Crook1, Bridget M. Lumb1 and Richard Apps1*

1 School of Physiology and Pharmacology, Medical Sciences Building, University of Bristol, University Walk, Bristol, UK
2 School of Physiology and Pharmacology, Medical Sciences Building, University of Bristol, University Walk, Bristol, UK

How does the cerebellum, the brain’s largest sensorimotor structure, contribute to complex behaviors essential to survival? While we know much about the role of limbic and closely associated brainstem structures in relation to a variety of emotional, sensory, or motivational stimuli, we know very little about how these circuits interact with the cerebellum to generate appropriate patterns of behavioral response. Here we focus on evidence suggesting that the olivo-cerebellar system may link to survival networks via interactions with the midbrain periaqueductal gray, a structure with a well-known role in expression of survival responses. As a result of this interaction we argue that, in addition to important roles in motor control, the inferior olive, and related olivo-cortico-nuclear circuits, should be considered part of a larger network of brain structures involved in coordinating survival behavior through the selective relaying of “teaching signals” arising from higher centers associated with emotional behaviors.

Keywords: cerebellum, inferior olive, periaqueductal gray, survival, modules

INTRODUCTION

A neural network of structures including, but not confined to, components of the limbic system (e.g., prefrontal cortex, amygdala, and hypothalamus) and closely linked brainstem structures (e.g., periaqueductal gray, PAG), are known to play a critical role in coordinating functions essential for survival, including a variety of emotionally related defensive behaviors triggered by aversive (e.g., fearful) or painful events (Bandler et al., 2000; Sokolowski and Coorbin, 2012). Historically, considerable attention has been devoted to mapping activity within different components of these “survival circuits” in relation to a variety of sensory, emotional, or motivational stimuli (cf. LeDoux, 2012). In marked contrast, we know much less about how these circuits interact with the motor system to generate appropriate patterns of behavioral response. The aim therefore of this short review is to discuss evidence, including recent observations, which together suggest that the concept of survival circuits should be extended to include the olivo-cerebellar system. In particular, we will focus on cerebellar interactions with the PAG; a structure with a well-characterized role in survival behaviors.

PAG AND SURVIVAL

The PAG is generally accepted to be a pivotal component of a central “survival network.” It is a behaviorally important source of descending control that is activated in response to a variety of emotional and environmental stressors, such as fear, anxiety, and pain (Bandler et al., 1991), and is crucial in controlling the expression and co-ordination of responses in these contexts (Fanselow et al., 1991; Carrié et al., 1997; Walker and Carrié, 2003). These controls include cardiovascular regulation, sensory modulation and the generation of a variety of emotionally related motor behaviors, such as fight-flight or immobility/withdrawal from the environment (commonly known as active and passive coping, respectively). Active coping enables an animal to escape a stressor (e.g., brief acute pain or encounter with a predator), and is elicited from a column of neurons situated in the dorsolateral/lateral (dl/l) functional column of the PAG. Activation of dl/lPAG increases arterial blood pressure, increases mobility (fight-or-flight responses) and elicits characteristic defense postures, e.g., the animal displays “reactive immobility” in that it is tense and ready for action but is temporarily motionless (Carrié, 1993; Lovick, 1993; Bandler and Shipley, 1994; Fendt and Fanselow, 1999; Kray and Bandler, 2001; Lumb and Leith, 2007). The dl/lPAG can be further divided into rostral and caudal segments with distinct defensive responses associated with upper and whole body movements, respectively (Bandler et al., 1991). By contrast, passive coping is characterized by a general disengagement from the environment when a stressor is inescapable (e.g., chronic pain) or when evading detection during close encounter with a predator. Passive coping is coordinated by a column of neurons located in ventrolateral (vl) PAG and is associated with a reduced responsiveness to external stimuli, and a general cessation in movements and a fixed (freezing) posture (Zhang et al., 1990; Bandler et al., 1991; Carrié, 1993; Lovick, 1993; Bandler and Kray, 1996). As part of these complex coping strategies, the PAG exerts descending control of spinal sensory processing that not only discriminates between nonxious and nonnoxious events but also between nociceptive inputs of different behavioral significance; C-nociceptor-evoked activity (mediating the slowly conducted, poorly localized and therefore distinction-sensitive nociceptive input) is depressed while A-nociceptor-evoked activity (the rapidly conducted component) that encodes the intensity of the nociceptive signal; McMullan and Lumb, 2006b) is left intact or even enhanced.

*Correspondence: Richard Apps, School of Physiology and Pharmacology, Medical Sciences Building, University of Bristol, University Walk, Bristol BS8 1TD, UK.
E-mail: r.apps@bristol.ac.uk
studies indicate that this pattern of effects could operate as part of both active and passive coping strategies that are co-ordinated by the dL5 and v6-PAG, respectively. Therefore, in both situations differential control of A- vs C-fiber-evoked activity could preserve the detailed information of changes in the external environment that can drive motivational behaviors and accurately direct motor activity (A-fibers), whilst depressing those components of the nociceptive message (C-fibers) that are less useful in terms of survival (e.g., enabling escape behavior without the distraction of C-fiber mediated pain; Wiers and Lamb, 1997; McMullan and Lamb, 2006a; Koutsioukis et al., 2007; Heinricher et al., 2009; Leith et al., 2010).

In summary, outputs from the different functional columns in the PAG co-ordinate fundamentally different patterns of autonomic adjustment, sensory regulation and motor responses that are highly dependent on the behavioral significance of the environmental, emotional or sensory stimulus.

In terms of PAG function, attention to date has focused on neural pathways that underlie autonomic regulation and sensory control, and polysynaptic descending paths that modulate autonomic outflow and sensory processing at the level of the spinal cord are well described (Lovick and Bandler, 2005). In contrast, much less is known about the neural pathways and mechanisms that link PAG activity to distinct patterns of motor responses. Until recently (Cermiñara et al., 2009; see below) we knew very little about whether descending control extends to sensory signals that feed into (and can modify) supraspinal motor circuits that control, and polysynaptic descending paths that modulate autonomic regulation and sensory signals.

EVIDENCE OF A PAG – CEREBELLAR LINK

Given the key role of the PAG in survival circuits, interactions with the cerebellum may provide an important mechanism through which co-ordinated movements can be modulated to enhance survival behaviors in aversive or threatening situations. Anatomical mapping studies provide at least some evidence that interconnections exist between the PAG and cerebellum. Direct, bilateral projections from vPAG to the cerebellar cortex were first described by Dietrichs (1983). The diffuse nature of the projection suggests the pathway most likely terminates as mossy fibers. In addition, several lines of anatomical evidence suggest that the PAG has links with the cerebellum via the inferior olive – climbing fiber system. Several studies have noted the presence of an ipsilateral projection from the PAG to the olive, including the caudal medial accessory olive (cMAO, Rutherford et al., 1984; Holstege, 1988). This region of the olive provides climbing fiber projections to the cerebellar vermis (Apps, 1990). The presence of such connectivity has been confirmed by using modern viral vector tracer techniques, which have the advantage over conventional tracers in that the
results are not confounded by tracer uptake by axons of passage (Flavell, 2008). In brief, by using targeted microinjections of green fluorescent protein (GFP) tagged adeno-associated virus-cytomegalovirus-enhanced GFP (AAV-CMV-eGFP) into vPAG, Flavell (2008) demonstrated a widespread but diffuse projection to all major subdivisions of the olive (see Figure 1A). Electrophysiological mapping studies have also shown that microstimulation in dorsal PAG elicits large field potentials localized to cerebellar vermis lobules VII/VIII – which have well defined roles in the control of oculomotor and cardiovascular functions (Noda and Fujikado, 1987; Nisimaru, 2004; Voogd and Barmack, 2006) – with a mean onset latency of 15.2 ± 0.8 ms (n = 5 rats, three trials per rat; Crook et al., unpublished observations; see Figures 1B,C). The waveform and trial-by-trial fluctuations in size of these evoked field potentials are typical of climbing fiber mediated responses (Armstrong and Harvey, 1968).

What role might the PAG link with the olivo-cerebellar system serve? In attempting to address this question there are two points worth noting. First, climbing fiber afferents, which terminate in a range of cerebellar cortical zones, are powerfully activated by nociceptive inputs (Ekerot et al., 1987). Second, climbing fiber pathways originating from the spinal cord (spino-olivocerebellar...
paths, SOCPs) are subject to central modulation during motor learning and active movements (Apps, 1999). Given the well known role of the PAG in regulating transmission of nociceptive signals at the level of the spinal cord, this raises the possibility that the link with the olivo-cerebellar system serves a similar function.

To test this possibility Cerminara and colleagues (2009) electrically stimulated the hindlimb and recorded climbing fiber field potentials in the C1 zone of the ipsilateral copula pyramidis of anesthetized rats, and found that the size of the evoked cerebellar responses (generated as a result of transmission in SOCPs) could be significantly reduced by chemical neuronal activation of vlPAG (Figure 2). The climbing fiber responses evoked in this region of the cerebellar cortex are relayed by two SOCPs; one conveys ascending signals via the dorsal funiculus, the other via the ventral funiculus (Oscarsson, 1969; Armstrong et al., 1973; Oscarsson and Sjolund, 1977a,b,c). Importantly, responses evoked by electrical stimulation of the dorsal or ventral funiculus were also reduced by PAG activation (Figure 2). This demonstrates that modulation of SOCPs by the PAG must, at least in part, occur supraspinally.

Direct anatomical projections from the PAG to the olive may have a role in this control, but this of course does not exclude the possibility that other (indirect) pathways are also involved. Descending connections to the PAG from higher structures such as the prefrontal cortex (Beitz, 1982; Kray and Bandler, 2001), may also be a route through which neocortical centers that are involved in emotionally related behavior can gain access to the olivo-cerebellar system. The finding that electrical stimulation of the prelimbic subdivision of rat prefrontal cortex powerfully drives activity in olivo-cerebellar pathways supports this hypothesis (Watson et al., 2009).
CEREBELLAR OUTPUT TO SURVIVAL CIRCUITS

Important insights into cerebellar contributions to survival circuits can also be gained from anatomical/physiological analysis of cerebellar output (cf. Strick et al., 2009). In particular, several lines of evidence suggest the cerebellar fastigial nucleus has links with limbic structures involved in survival behaviors, such as the hippocampus, hypothalamus, ventral tegmental area (VTA), and amygdala (e.g., Snider and Minti, 1976; Newman and Reza, 1979; Cao et al., 2013). In respect to cerebellar-PAG projections, Whiteside and Snider (1953) showed that electrical stimulation of vermal lobule VII in the anesthetized cat can evoke responses in the dorsal PAG with two distinct latencies (2–3 ms and 8–12 ms), which raises the possibility that multiple cerebellar-PAG pathways exist. Consistent with a direct (short latency) projection, anatomical tracing studies have shown the existence of efferent fastigial projections to the PAG in a number of species (Martin et al., 1974) in the opossum; Reitz (1982); Gonzalez-Ruiz and Leichtnitz (1987), Gonzalez-Ruiz et al. (1990) and Teune et al. (2000) in the rat, and Gonzalo-Ruiz et al. (1988) in monkey. Many of these studies have advanced the view that the projections subserve an oculomotor function. However, it is possible that functions of fastigial-PAG projections are more widespread and enable the powerful computational circuitry of the cerebellum to engage with circuits related to the expression of survival behaviors. Consistent with this proposal, clinical studies have shown that chronic stimulation of the cerebellar vermis can have effects on motor and nonmotor symptoms, such as drowsiness (Fadiga et al., 1968; Giannuzio et al., 1968a,b; Manzoni et al., 1968), aggression (Reis et al., 1973), and grooming behavior (Bernston et al., 1979; Cao et al., 2013). In respect to cerebellar-PAG projections, the functional significance of olivo-cerebellar involvement in this network remains to be determined, but one influential theory of climbing fiber function is that they serve a teaching role (for a review see for example Yeo and Henslow, 1998). The powerful climbing fiber mediated projection from PAG to the cerebellum and gaging of SOCPs by the PAG may be considered in relation to this theory. Under appropriate behavioral conditions in which survival circuits are engaged, the gaging may reflect a switch from the usefulness of learning signals derived from the periphery, to allowing signals arising from higher centers to modify cerebellar function.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Biotechnology and Biological Sciences Research Council, UK. We thank Louise Hickey and Lianne Leith for contributions to the viral tracing and electrophysiological mapping experiments.

REFERENCES

Armstrong, D. M. (1986). Supraspinal organization of the inferior olive: projection to the posterior lobe of the rat cerebellum. J. Comp. Neurol. 282, 236–254. Apps, R. (1990). Columnar organization of the inferior olive, projection to the posterior lobe of the rat cerebellum. J. Comp. Neurol. 302, 236–254. Apps, R. (1998). Movement-related gating of climbing fibre input to cerebellar cortical zones. Prog. Neurobiol. 57, 537–562. Apps, R. (2000). Rostrocaudal branching within the climbing fibre projection to forelimb–receiving areas of the cerebellar cortical Cl zone. J. Comp. Neurol. 418, 193–204. Apps, R., and Garwicz, M. (2005). Anatomical and physiological foundations of cerebellar information processing. Nat. Rev. Neurosci. 6, 295–311. Apps, R., and Hawks, B. (2009). Cerebellar cortical organization: a somatotopic hypothesis. Nat. Rev. Neurosci. 10, 670–681. Armstrong, D. M. (1986). Supraspinal contributions to the initiation and control of locomotion in the cat. Prog. Neurobiol. 26, 275–381. Armstrong, D. M., and Harvey, R. J. (1988). Responses to a spino–olivo–cerebellar pathway in the cat. J. Physiol. 447, 147–168. Armstrong, D. M., Harvey, R. J., and Schild, B. F. (1975). Branching of inferior olivary axons to terminate in different folia, lobules or lobes of the cerebellum. Brain Res. 80, 305–371. Bandler, R., Carpenter, P., and Zhang, S. P. (1991). Integration of somatic and autonomic reactions within the midbrain periaqueductal gray: visceral, somatomotor and functional organization. Prog. Brain Res. 87, 269–303. Bandler, R., and Keay, K. A. (1996). Columnar organization in the midbrain periaqueductal gray and the integration of emotional expression. Prog. Brain Res. 107, 269–303. Bandler, R., Keay, K. A., Flood, N., and Price, J. (2000). Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. Brain Res. Bull. 53, 95–104. Bandler, R., and Shipley, M. T. (1994). Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? Trends Neurosci. 17, 379–389.
Berntson, G. G., Potolicchio, S. J. Jr., and Reis, E. (1993). Cardiovascular and neuroendocrine responses to the cerebellar motor control system. Brain Res. Bull. 31, 405–418.

Cerebellar fastigial nuclear GABAergic neurons are involved in the regulation of cardiovascular and autonomic function. These neurons are critical for the control of blood pressure, heart rate, and other autonomic responses. Understanding the mechanisms underlying these responses can provide insights into the role of the cerebellum in the modulation of cardiovascular function.

However, the exact mechanisms responsible for the cerebellar modulation of cardiovascular function are not fully understood. Further research is needed to elucidate these mechanisms and their clinical relevance.

References:

- Berntson, G. G., Potolicchio, S. J. Jr., and Reis, E. (1993). Cardiovascular and neuroendocrine responses to the cerebellar motor control system. Brain Res. Bull. 31, 405–418.

- Berntson, G. G., Potolicchio, S. J. Jr., and Reis, E. (1993). Cardiovascular and neuroendocrine responses to the cerebellar motor control system. Brain Res. Bull. 31, 405–418.

- Berntson, G. G., Potolicchio, S. J. Jr., and Reis, E. (1993). Cardiovascular and neuroendocrine responses to the cerebellar motor control system. Brain Res. Bull. 31, 405–418.
Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J. Neuropsychiatry Clin. Neurosci. 16, 367–378.

Schutter, D. J., Enm, D., and Hoppenbrouwers, S. S. (2009). High-frequency repetitive transcranial magnetic stimulation to the cerebellum and implicit processing of happy facial expressions. J. Psychopathol. Neuropsychiatry 34, 40–45.

Schutter, D. J., Laman, D. M., Van Honk, J., Vingron, A. C., and Koerselman, G. F. (2009b). Partial clinical response to 2 Hertz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. J. Psychiatry Neurosci. 34, 60–65.

Shirota, D. J., and van Honk, J. (2005). The cerebellum on the rise in human emotion. Cerebellum 4, 290–294.

Sokolowski, K., and Corbit, J. G. (2012). Wiring for behaviors: from development to function of innate limbic system circuitry. Front. Mol. Neurosci. 5:55. doi: 10.3389/fnmol.2012.00055

Strata, P., Scelfo, B., and Sacchetti, B. (2011). Involvement of cerebellum in emotional behavior. Physiol. Res. 60(Suppl.1), S39–S48.

Strata, P., Scelfo, B., and Sacchetti, B. (2004). Long-term synaptic plasticity in the cerebellar anterior lobe. Exp. Brain Res. 28, 489–496.

Sacchetti, B., Scelfo, B., Tempia, F., and Strata, P. (2007). Reversible inactivation of the cerebellar nuclei. J. Cereb. Blood Flow Metab. 28(Suppl. 2), 285–300.

Sokolowski, K., and Corbit, J. G. (2012). Wiring for behaviors: from development to function of innate limbic system circuitry. Front. Mol. Neurosci. 5:55. doi: 10.3389/fnmol.2012.00055

Strata, P., Scelfo, B., and Sacchetti, B. (2011). Involvement of cerebellum in emotional behavior. Physiol. Res. 60(Suppl.1), S39–S48.