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Involvement of the cerebellum in the serial reaction time task (SRT) (Response to Janacsek et al.)

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A B S T R A C T

An ALE meta-analysis focused on the serial reaction time task published in NeuroImage (Janacsek et al., 2019) demonstrated consistent activation of the basal ganglia across neuroimaging studies featuring sequence > random block contrasts and no consistent cerebellar activation. To enable valid conclusions regarding the role of the cerebellum in this context, some of the included studies should be excluded (e.g., because the cerebellum was explicitly not scanned). After omitting 6 of 16 studies/subject groups, 70% of the remaining studies did report cerebellar activation. While an ALE analysis of the remaining contrasts confirmed the original results, it may lack the power to detect cerebellar effects. We argue the conclusion that the cerebellum is not involved in sequence-specific learning should be treated with caution.

An ALE meta-analysis of 20 neuroimaging studies focusing on the serial reaction time (SRT) task (Janacsek et al., 2019) appeared in a recent issue of NeuroImage. We read this study with great interest, as the authors have combed through a vast literature with careful consideration of experimental and control conditions that was lacking in previous reviews (e.g., Bernard and Seidler, 2013; Hardwick et al., 2013), likely driven by a limited number of comparable studies at that time. Further, they pay due attention to the role of the cerebellum, a brain region that has historically been overlooked in cognitive neuroscience (Schmahmann, 2010). Their quantitative review reveals a core basal ganglia network (nucleus caudatus, globus pallidus and putamen) involved in sequence learning.

To briefly reiterate, in a classical SRT task, participants have to respond as fast as possible to the location of sequentially presented visual stimuli, appearing e.g. in one of four locations. Typically unbeknownst to the participants, there is a sequential regularity in the target locations. After a number of sequenced blocks, the sequential structure is replaced by a (pseudo-)random order. The resulting increase in reaction times (relative to regularly sequenced blocks) is traditionally used to quantify sequence specific learning. Hence, Janacsek et al. (2019) primarily focused on the comparison of brain activity during sequence blocks versus random (baseline) blocks. However, many studies have employed less well-matched baseline conditions than random blocks (e.g. simple finger tapping). Comparing sequence blocks to *all* baseline conditions, Janacsek et al. (2019) found consistent activation in the basal ganglia, premotor cortex (BA6) and the cerebellum across studies. Narrowing their focus to the more strictly matched comparison of sequenced versus random blocks (listed in Table 1), they only found consistent activation in the basal ganglia. Therefore, they concluded that the cerebellum is "*involved not in sequence learning itself (i.e., the acquisition of sequential order), but rather in other functions that support sequence learning" (p.9).*

In stark contrast, sequence learning has been described as a basic cerebellar function (e.g., D'Angelo and Casali, 2012). After careful investigation of the source data, we believe that the conclusion regarding the cerebellum of Janacsek et al. (2019) should be treated with reservation, as we believe a number of studies should be excluded for an analysis regarding the cerebellum.

First and foremost, to enable any valid inference about the consistency of cerebellar activation across studies, *inclusion should be restricted to studies measuring, analyzing and reporting significant cerebellar activation (if any) in the first place.* Perhaps due to historic resistance against the idea of a "cognitive cerebellum" (Schmahmann, 2010), the cerebellum is often neglected in cognitive neuroimaging data acquisition and analysis. As a case in point, we believe that 3 studies/subject groups in the review of Janacsek et al. (2019) should be excluded on these grounds (Landau & D'Esposito, 2006; Werheid et al., 2003; Zedkova et al., 2006). In particular, Werheid et al. (2003) explicitly state they did not scan the cerebellum in their protocol (featuring an axial depth of 8.4 cm). While it is impossible to tell conclusively based on the description of the scanning protocol alone, it seems unlikely that another study, featuring an even more limited axial depth of 8.1 cm (Landau & D'Esposito, 2006), could capture activation across the whole cerebral cortex and the cerebellum (mean axial depth across protocols = 11 cm, see Table 1). Lastly, Zedkova et al. (2006) restricted their statistical analysis a priori to the cortex, thalamus, nucleus caudatus and putamen.

Second, in our opinion, three other studies (Bischoff-Grethe et al.,

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Table 1
Overview of included SRT neuroimaging studies.

Study	*N*	Cerebellar activation (Talairach & Tournoux)			Notes	Axial depth cfr. protocol (cm)
Landau & D'Esposito (2006)	8	/			Scan protocol likely excluded cerebellum.	8.1
Werheid et al. (2003)	7	/			Scan protocol explicitly excluded cerebellum.	8.4
Zedkova et al. (2006)	15	/			Analysis protocol excluded cerebellum.	10
Purdon et al. (2011)	17	/			Contrast includes first episode schizophrenics	10
Bischoff-Grethe et al. (2001)	20	/			Contrast is parametric/SVC-based	12
Poldrack et al. (2005)	14	/			Contrast is SVC-based	9.5
Ettinger et al. (2013)	26	/				12.4
Naismith et al. (2010)	20	/				12
Rauch et al. (1997a)	9	/				9.75
Daselaar et al. (2003)	26	18	−78	−15		12.6
Dennis & Cabeza (2011)	12	8	−52	−4		12.9
Doyon et al. (1996)	14	12	−59	−24		9
Heun et al. (2004)	10	−33 36	−39 −42	−45 −48		13.8
Kumari et al. (2002)	6	−29	−64	−18		10.1
Rauch et al. (1997b)	10	−3	−57	6		12
Willingham et al. (2002) contrast: explicit	18	−30 33	−62 −68	−22 −14		12
contrast: implicit			/			

2001; Poldrack et al., 2005; Purdon et al., 2011) don't seem to meet the original inclusion criteria. Janacsek et al. (2019) employed three main inclusion criteria; studies should: 1) concern functional imaging data and use a whole-brain analysis approach, 2) present data from healthy, non-elderly adults and 3) employ a classic visuomotor SRT task. After assessment of the resulting studies, the final set was narrowed down to 4) studies reporting significant activations in the key contrast of sequence compared to baseline. According to our reading, the reported 13 foci of one study are derived from an analysis collapsing across healthy controls and first episode schizophrenics (Purdon et al., 2011), thus violating criterion 2. This is particularly problematic given the evidence of cerebellar abnormalities in schizophrenics, including hypoactivation (e.g., Andreasen and Pierson, 2008; Yeganeh-Doost et al., 2011). Note that other clinical group contrasts (e.g. the depressed group in Naismith et al., 2010) *were* excluded from analysis. Perhaps less clear-cut, another study reported no significant activation at all in a whole brain analysis of a sequence > random contrast (Poldrack et al., 2005), which violates criterion 4. We assume that the single reported focus from Poldrack et al. (2005) refers to the marginally significant nucleus caudatus activation that reached statistical significance after small volume correction (SVC), which should not be included, based on criterion 1. Lastly, the three foci from a study by Bischoff-Grethe et al. (2001) are derived from a linear parametric analysis correlating brain activation to predictability of a visuospatial sequence. While two out of three levels in this analysis correspond to sequence (fully predictable) and random (totally unpredictable), an intermediate level of predictability (Markov chain probabilistic sequence) was also included in the model. Further, SVC was again applied for some regions (i.e., nucleus caudatus), but not for the cerebellum. As such, this study violates criteria 1 and 4.

Based on this review, 6 out of 16 (38%) included studies/subject groups, corresponding to 81 out of 232 subjects (35%), should be excluded. Given that studies featuring the crucial sequence > random comparison in an SRT task context are sparse, inclusion of these studies is certainly defensible to study cerebral activation, but at the same time it undermines the validity of any resulting claims regarding cerebellar functions. Crucially, a reanalysis of the remaining 10 subject groups contrasts may be underpowered for effect sizes below ~0.45 (Eickhoff et al., 2016; Janacsek et al., 2019). Nonetheless, we conducted an ALE-analysis using GingerALE 3.0.2 (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012), using the same parameters to determine statistical significance. ALE input was organized per subject group, limiting the impact of studies with multiple contrasts (Turkeltaub et al., 2012), so that the reanalysis concerns 10 studies/subject groups, but 11 contrasts (2 contrasts from the same subject group in Willingham et al. (2002) were included). Reassuringly, the outcome confirmed the main conclusion of Janacsek et al. (2019): bilateral activation of the basal ganglia, in absence of any other significant activation.

Nevertheless, a majority of 7 out of the 10 remaining studies report cerebellar activation, while 9 out of 10 report basal ganglia activation (all except Heun et al., 2004). In comparing this (rough) statistic, it is relevant to note that signal-to-noise ratio is relatively low in the cerebellum and assessment of cerebellar activation by typical MRI protocols is generally less reliable compared to cerebral activations (Marek et al., 2018; Schlerf et al., 2014). The considerable variability in the localization of the cerebellar activations (see Table 1) is apparently too large to result in a consistent ALE-cluster across studies. As a case in point, of the 7 subject groups demonstrating cerebellar activation in our reanalysis, only two (Kumari et al., 2002; Willingham et al., 2002) contributed to the left cerebellar lobule VI cluster in Janacsek et al. (2019) (sequence > all baselines). However, there are several arguments not to dismiss these activations as random too readily.

First, it is possible that the distributed cerebellar activation peaks reflect distinct functional contributions. As outlined above, the limited number of studies may then be underpowered to detect these distinct activations. For example, subdivisions of the cerebellum may exhibit different contributions in early versus late SRT learning (D'Angelo and Casali, 2012; Doyon et al., 2002; Penhune and Steele, 2012). All contrasts included by Janacsek et al. (2019) probed the first day of training (early learning). Even so, there was substantial variation in the amount and nature of pre-scan training (e.g., 1600 trials sequence only, Doyon et al., 1996; 1728 trials mixed conditions, Willingham et al., 2002; 2 minutes of random blocks only, Daselaar et al., 2003; no pre-scan training at all, Dennis and Cabeza, 2011). Degree of training before scanning may therefore be one source of variability in cerebellar activation locations.

Second, classically applied procedures and templates result in relatively poor alignment of cerebellar activations (Diedrichsen, 2006; Schlerf et al., 2014), which may result in larger localization variability, rendering them "vulnerable" in the context of the ALE methodology.

More fundamentally, it seems disputable that neural activation correlated with sequence learning is best captured by larger *persistent* activation during sequence than random blocks. Indeed, learning essentially entails a change over time, and several studies have therefore looked at consistently increasing or decreasing activation over time (sequence > random) to capture sequence learning related brain activation, and at least some have shown cerebellar involvement (e.g., Rose et al., 2011; for a meta-analytic review, see Lohse et al., 2014). Such contrasts were investigated by Janacsek et al. (2019) in a separate analysis, but yielded no significant ALE results, possibly due to the low number of studies.

Cerebellar processes undeniably influence SRT learning, as evidenced, e.g., by the impact of cerebellar tDCS on SRT learning (Ehsani et al., 2016; Ferrucci et al., 2013). Janacsek et al. (2019) suggest that this influence is auxiliary, e.g., related to attention processes reflecting explicit knowledge or insufficiently controlled attentional demand differences between sequence and baseline conditions. Likewise, several experimental studies have concluded that the role of the cerebellum is restricted to retention and automatization/performance modification in sequence learning (e.g., Hikosaka et al., 1998; Nixon and Passingham, 2000; Seidler et al., 2002). However, several other studies have, to the contrary, found that the cerebellum plays an essential role in sequence detection and acquisition per se (e.g., Doyon et al., 1996; Molinari, 1997; Steele and Penhune, 2010). Of note, Janacsek et al. (2019) relate the essential contribution of the basal ganglia in sequence acquisition to prediction-feedback processes, a function that has been attributed to the cerebellum by others (e.g., Doya, 2000). A detailed discussion of the possible role of the cerebellum vis-à-vis basal ganglia in sequence learning is beyond the scope of this brief comment; for reviews, see (Bostan and Strick, 2018; Doya, 2000; Doyon et al., 2009; Hikosaka et al., 2002; Penhune and Steele, 2012).

To summarize, the review by Janacsek et al. (2019) clearly demonstrates the robust involvement of the basal ganglia in sequence learning. Even after excluding 6 of the original 16 subject groups which we deem unsuitable to assess the possible contribution of cerebellar versus basal ganglia mechanisms, the ALE analysis confirmed the original conclusions (robust basal ganglia activation in absence of consistent cerebellar activation across studies). However, given a) the observation that 70% of the remaining studies *did* report cerebellar activation, b) that the confirmatory ALE analysis of the remaining 10 studies may lack power to detect functionally distinct cerebellar contributions, and c) reservations regarding the contrast of interest as the best choice to measure sequence specific *learning*, we believe that their conclusion that the cerebellum is not involved in sequence-specific learning should be treated with caution. In general, like Janacsek et al. (2019), future meta-analyses of cognitive neuroimaging should not overlook the role of the cerebellum. This requires very meticulous examination of the experimental methods, as a substantial number of neuroimaging studies has not measured or investigated cerebellar activation.

Declaration of competing interest

None.

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