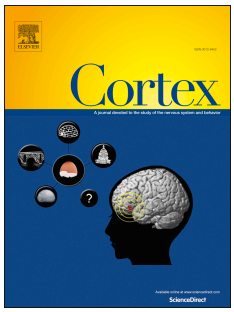

Maybe causal, but still cautious: Reply to “Cautious or causal? Key implicit sequence learning paradigms should not be overlooked when assessing the role of DLPFC (Commentary on Prutean et al.)”

Nicoleta Prutean, Elisa Martín-Arévalo, Alicia Leiva, Luis Jiménez, Antonino Vallesi, Juan Lupiáñez

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Maybe causal, but still cautious: Reply to "Cautious or causal? Key implicit sequence learning paradigms should not be overlooked when assessing the role of DLPFC (Commentary on Prutean et al.)"

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Authors contribution

N.P. – Conceptualization, Writing – Original draft, Visualization; E.M.A. – Conceptualization, Supervision; A.L. – Conceptualization, Supervision; L.J. – Conceptualization, Writing – Original draft, Writing – review and editing, Visualization, Supervision; A.V. – Conceptualization, Writing – review and editing, Supervision; J.L. – Conceptualization, Writing – Original draft, Writing – review and editing, Supervision, Project administration.

In our recent work (Prutean, Martín-Arévalo et al., 2021), we presented the existing evidence on the causal role of DLPFC top-down control on the acquisition and automatic expression of implicit sequence learning. Implicit sequence learning refers to the incidental acquisition of structured information, which is not accompanied by full awareness of its contents, but it gets automatically expressed in the appropriate context (Reber, 1993). The systematic review was motivated by previous studies suggesting an antagonistic role of cognitive control on the automatic expression of sequence learning (Jiménez et al., 2006; Jiménez et al., 2009; Prutean, Wenk et al., 2021; Vaquero et al., 2019), and by evidence on the role of DLPFC in engaging such a control function (Botvinick et al., 2001; Nee & D'Esposito, 2016).

Based on our selection criteria, we reported seven studies which had tackled the causal role of DLPFC on the *acquisition* of sequence learning. In addition, we pre-registered and ran an explorative study in which we inhibited the left and right DLPFC after learning acquisition, and expected to observe an increase in the *expression* of sequence learning. Importantly, five of those studies in the existing literature failed to find any evidence of DLPFC involvement on the acquisition of sequence learning and, against our pre-registered hypotheses, we reported evidence for the absence of any DLPFC involvement on the expression of sequence learning. Thus, considering the outcomes of these studies, and contrary to our expectations, we concluded that up to date there is not sufficient evidence supporting a causal role of DLPFC in modulating either the acquisition or the expression of sequence learning.

Whilst still standing behind this conclusion, we would like to thank Vékony and colleagues (2021) for their commentary, since it allowed us to think more deeply about the procedural differences between the paradigms in which DLPFC stimulation produced an effect on sequence learning (i.e., ASRT in Ambrus et al., 2017; Janacsek et al., 2015) and those which actually provided evidence for the absence of such effect (i.e., SRT in Prutean, Martín-Arévalo et al., 2021). In the review, we suggested that the significant modulation of implicit sequence learning by DLPFC stimulation in Ambrus et al., and Janacsek et al., should be taken cautiously, since those studies did not include any direct test for the implicitness of the learning process. However, Vékony and colleagues reported convincing evidence that the ASRT paradigm did not evoke explicit awareness of the trained sequence in previous studies which had directly assessed it. In addition, the authors advanced that the DLPFC contribution to sequence learning might be task-dependent, since it was observed just in the ASRT paradigm, and not, for instance, in the SRT paradigm.

As pointed out in our systematic review, we consider that up to date evidence in the literature is too scarce to draw any firm conclusion on the DLPFC contribution to implicit sequence learning, since very few studies have addressed this issue and mixed results have been reported so far (i.e., just two of eight studies observed a significant modulation). Moreover, we do not consider the direct comparison between the two studies implementing the ASRT task and our exploratory study with the probabilistic SRT task as adequate to draw any conclusion on DLPFC task-dependency, since these experiments not only differed in the paradigm used, but also in the stimulation timing, stimulation protocol, and stimulation site. Such research question goes beyond the scope of the manuscript, but future studies should equate these experimental procedures and statistical power in a within-subjects design in order to investigate DLPFC task-dependency in sequence learning.

However, to follow up Vékony and colleagues (2021)' suggestion, we agree that there are methodological characteristics that differentiate the two paradigms, in the sense that the sequence learning trained with either of them could be qualitatively different and, possibly, differently influenced by DLPFC stimulation as well.

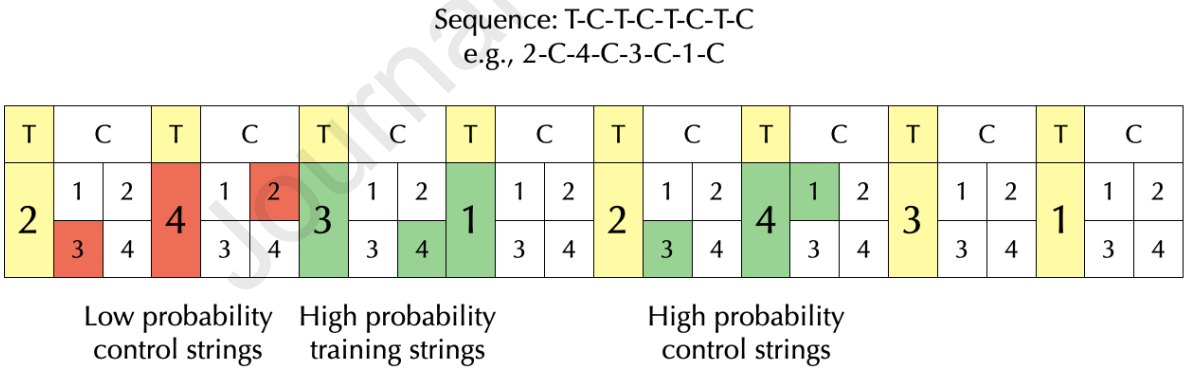

Figure 1. Sequential information in the ASRT task: the task alternates between high probability training strings on odd trials (3-4-1 transition in green) and low probability control strings on even trials (3-4-2 transition in red). However, some training strings are also presented on even trials (i.e., high probability control strings, as the 3-4-1 transition in green).

	ASRT task in (Ambrus et al., 2017 and Janacsek et al., 2015)	SRT task (in Prutean et al., 2021)
Frequency of trials	• 62.5 % training strings (50% on odd positions, 12.5% on even positions) • 37.5% control strings	• 80% training trials • 20% control trials
Predictiveness of trials	Alternated presentation: • Training strings occur on 100% of odd trials • Control strings occur on 87.5% of even trials	Probabilistic presentation: • Training and control trials are not predictable
Repetitions and alternations	• Single (AA) repetitions balanced between training and control strings • Double (AAA) repetitions and alternations (ABA) allowed exclusively on control strings	• Single (AA), and double (AAA) repetitions forbidden • Alternations balanced between training and control trials

Table 1. Comparison between ASRT and SRT paradigms

As shown in Figure 1, the ASRT paradigm alternates between training strings on odd trials (e.g., 3-4-1), and control strings on even trials (e.g., 3-4-2). Interestingly, training strings arise also on a quarter of even trials (i.e., high probability control strings, e.g., 3-4-1 transition), thus resulting in three types of trials overall: training trials on all odd trials, high probability control trials on some even trials (together computed as 62.5% training strings), and 37.5% low probability control trials on the remaining even trials. Thus, the ASRT paradigm presents overall 62.5% training trials compared to 80% training trials in the SRT task. However, Table 1 summarises other structural characteristics which differentiate the two paradigms beyond the

frequency of training trials. For instance, for the alternating nature of the task, the presentation of training trials is not probabilistic (as in the SRT paradigm), but it rather follows an alternating rhythm, which could possibly help to parse sequence learning. If the rhythmic structure would not contribute to sequence learning measurements, we could expect the same performance on training trials presented on odd positions (e.g., 3-4-1 transition) and those presented on even positions (e.g., high probability control, such as a 3-4-1 transition), since they represent the same exact frequent triplet. However, Kóbor and colleagues (2018) have previously reported that when the odd and even trials in the ASRT task were cued by different stimulus identities, participants were not only sensitive to the frequency of training trials, but also to the alternating structure of the task, as they were 100 ms faster to training trials presented as (frequent) odd trials compared to the exact same triplets but presented as (even) trials. Crucially, as we highlight in Table 1, salient strings such as a triple repetitions (e.g., 1-1-1) and alternations (1-2-1) arise exclusively on control trials in the ASRT paradigm. For the building principle of the task, these salient strings (on even trials) could cue the incoming information on odd trials, and further help participants to rhythmically parse the sequence in two alternating parts. To the best of our knowledge, the extent to which the rhythmic structure might bias sequence learning in the standard ASRT task has never been explicitly addressed nor captured by any kind of measure of awareness.

In addition, Vaquero et al. (2006) have already addressed the problems of alternations in assessing sequence learning. It appears that alternations can be learned very easily, but participants are slower in response to them compared to other trials, due to inhibition of return (Lupiáñez et al., 2013) and negative priming (Tipper, 1985). Therefore, as long as training and control trials do not have the same proportion of alternations (i.e., in the ASRT task), sequence learning measurements would be contaminated by these effects. Even if these trials are excluded from the analyses of sequence learning (as in Ambrus et al., 2017 and Janacsek et al., 2015), experiencing systematic slow responses due to alternations exclusively on control trials might bias participants to expect them throughout training and slow down responses accordingly (on even trials). This could further explain why Kóbor and colleagues (2018) have observed longer response times to training trials presented on even positions compared to the same strings but experienced on odd positions. Moreover, this would represent yet another strategic component in the ASRT task, which participants might learn (together with the rhythmic alternation) on top of the frequency information, and which could be indeed influenced by modulations of DLPFC top-down control.

To conclude, we accept Vékony and colleagues (2021)' suggestion that the implicitness of the sequential information as acquired throughout the ASRT task might not be the key to understand why DLPFC stimulation did have an impact on that paradigm compared to others sequence learning paradigms, such as the SRT task. We consider, however, that more research needs to be carried out in a controlled and preregistered way to draw any firm conclusion on DLPFC contributions to sequence learning in general, and to ASRT vs. SRT tasks in particular. For instance, in order to claim that DLPFC contributions to sequence learning are task-dependent, future studies should directly compare in a within-subjects design the ASRT task and SRT task with the same frequency information, stimulation and timing procedure, and it should further clarify which aspects of the ASRT task other than the 62.5% frequency information might influence sequence learning measurements, and therefore be susceptible of strategical DLPFC top-down control influences (Botvinick et al., 2001; Nee & D'Esposito, 2016). Crucially, to make strong claims on the causal role of DLPFC on sequence learning, such direct comparison should also incorporate a canonical task on which it has been clearly demonstrated an effect of inhibiting DLPFC with TMS (Friehs et al., 2020), especially if no effect is observed with either paradigm, as most of the studies reviewed by Prutean, Martín-Arévalo et al. (2021) would suggest.

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