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Letters to the Editor

A review of the evidence against the "first come first served" hypothesis. Comment on Truini et al. [Pain 2007;131:343–7]

When directed to the skin, heat pulses produced by infrared laser stimulators activate selectively Aδ and C nociceptors, and subjects report a dual sensation of first and second pain. However, laser-evoked brain potentials (LEPs) appear only in a time window compatible with the conduction velocity of Aδ fibers [4]. When the concomitant activation of Aδ nociceptors is avoided, both the perception of first pain and the Aδ LEP disappear. More surprisingly, this also leads to the appearance of brain responses in a time window compatible with the conduction velocity of C fibers [20].

In a study published in the November issue of Pain, Truini et al. [23] designed an experiment to investigate if this phenomenon depends on the order of arrival of somatosensory inputs to the cortex. They used pairs of laser stimuli to reverse artificially the usual order of arrival of Aδ and C afferent volleys. They observed that following a conditioning C afferent volley, the cortical response to a second afferent volley, whether Aδ or C, was significantly reduced. This reduction was stronger at shorter inter-stimulus intervals, and more pronounced when the test response was elicited by C stimuli. These results broaden some of their previous findings: when two consecutive Aδ stimuli or two consecutive Aβ stimuli are applied, the response elicited by the second stimulus is reduced, and this reduction is more pronounced for the responses elicited by Aβ stimuli [24].

Truini et al. interpreted these results as evidence that "only the earliest of a series of somatosensory volleys elicits cerebral responses synchronous enough to yield ERPs", thus supporting the hypothesis that Garcia-Larrea [12] had christened as "first come first served".

We believe that this interpretation is incorrect. Indeed, the results reported by Truini et al. can be entirely explained by the modulation of a crucial confounding factor that was not taken into account when they designed their experiments. This confounding factor is stimulus expectancy, one of the main determinants of the saliency of any sensory stimulus. In both their 2004 and their 2007 study, Truini et al. presented the pairs of stimuli in blocks. Within each block, the inter-pair interval (IPI) was randomly varied across trials (between 10 and 30 s), while the inter-stimulus interval (ISI) within each pair was identical across trials. In other words, the conditioning stimulus of each pair occurred after a random amount of time, while the test stimulus of each pair occurred after a constant amount of time. Consequently, the occurrence of the second stimulus of each pair was, within each block, much more *expected* than the occurrence of the first stimulus (Fig. 1, upper panel). Therefore, it could well be that the amplitude reduction of the test response observed in both studies was merely a consequence of the increased expectancy of the test stimulus, and not a consequence of "order of arrival" of afferent volleys, "refractoriness" or "relative refractoriness of sensory networks generating LEPs". The reported results would have constituted evidence supporting the "first come first served" hypothesis *if and only if* the observed amplitude reduction of the test response was still present when the second stimulus of the pair was as unexpected as the first one. This could have been easily achieved by randomizing the ISI from trial to trial (Fig. 1, lower panel).

As a matter of fact, results of previous studies clearly indicate that if Truini et al. had used an experimental design that accounted for stimulus expectancy, the outcome of their studies would have been completely different. Indeed, in a study published in Pain [17], we showed that when the test stimulus of a pair of laser stimuli is as unexpected as the conditioning stimulus, the response to the test stimulus is *entirely unaltered* even at ISIs as short as 280 ms, thus conclusively ruling out refractoriness in the Aδ pathway (and the "first come first served" hypothesis). It is important to note that our results do not constitute an isolated finding. They simply show that LEPs obey a rule that is common to all vertex potentials: when pairs of stimuli of the same sensory modality (whether somatosensory, auditory or visual) are delivered at constant ISI, the response elicited by the test stimulus is *always* smaller than that elicited by the conditioning stimulus [1–3,5,6,8–11,13,14,16,18, 21–24]. In contrast, when pairs of stimuli are delivered at variable ISI, the response elicited by the test stimulus is *always* similar (or even greater) than that elicited by the conditioning stimulus [7,15,17,19].

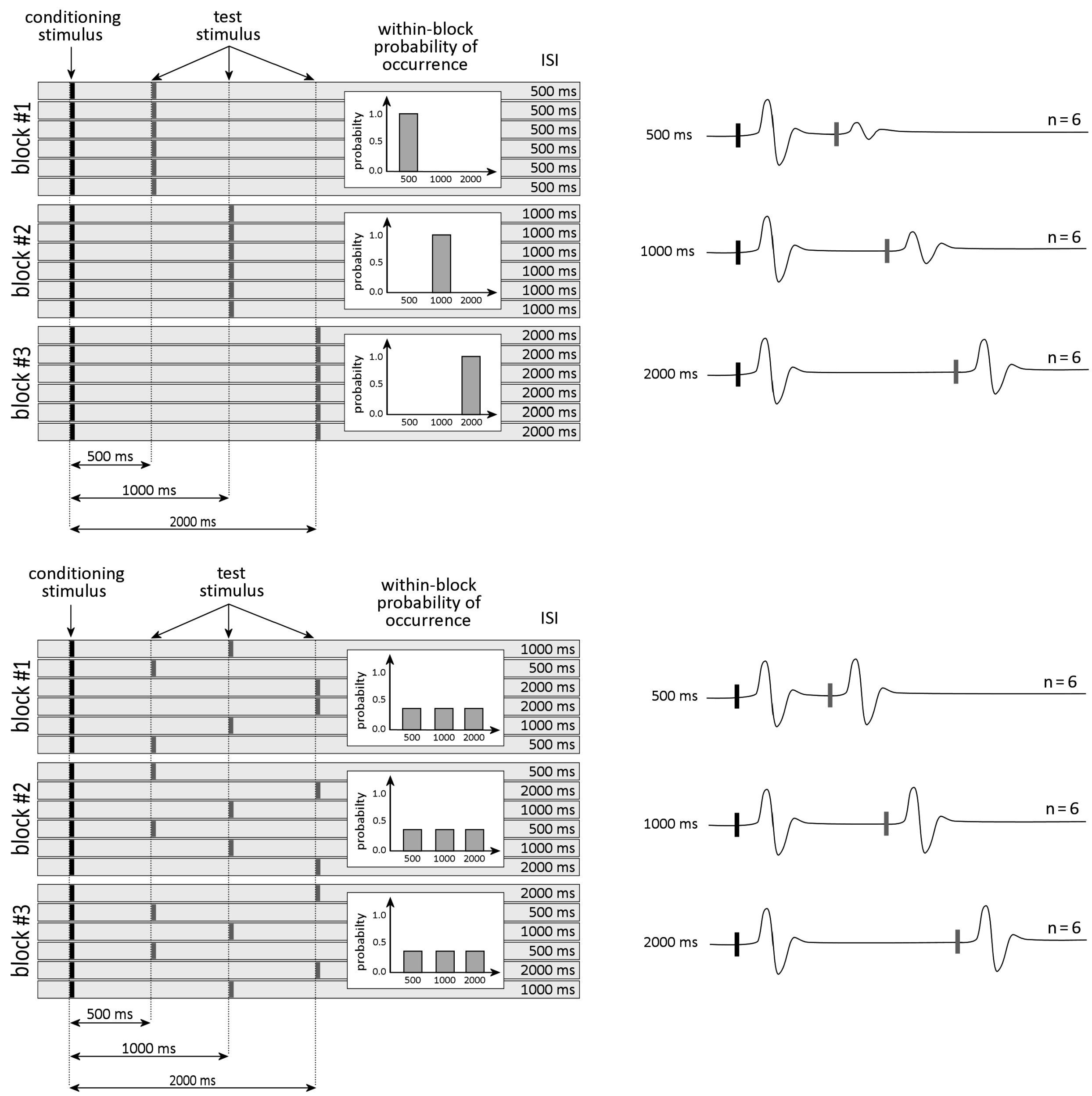

Fig. 1. Two possible experimental paradigms to explore the effect of inter-stimulus interval (ISI) on the brain potentials elicited by pairs of identical stimuli. In the paradigm outlined in the upper panel, the ISI is *identical* across the trials of each block. Therefore, the test stimulus is much more expected than the conditioning stimulus. ERP experiments performed using a similar paradigm [1–3,5,6,8–11,13,14,16,18,21–24] have shown a reduction of the amplitude of the vertex potentials elicited by the test stimulus, stronger at short ISIs (right graphs, simulated data). In contrast, in the experimental paradigm outlined in the lower panel, the ISI is varied randomly across the trials of each block. Therefore, the expectancy of the test stimulus is much more matched to the expectancy of the conditioning stimulus. ERP experiments performed using such a paradigm [7,15,17,19] have shown that the amplitude of the vertex potentials elicited by the test stimulus is similar to (or even larger than) the amplitude of the response elicited by the conditioning stimulus (right graphs, simulated data).

When comparing all these results, it becomes evident that the magnitude of vertex potentials is not conditioned by the order of arrival of afferent volleys to the central nervous system, but by their respective temporal expectancy. Using the same metaphorical language of Truini et al., what is "served" (by a large-amplitude brain response) is not necessarily the stimulus that "comes first", but the stimulus that is less expected. Obviously, in an experimental paradigm where stimuli are presented with a constant ISI across trials, the "first come" stimulus is unavoidably less expected (and hence more salient) than the following one.

For all these reasons, the results reported by Truini et al. do not support the existence of a "first come first served" mechanism for the generation of vertex potentials. Instead, they provide additional evidence that temporal expectancy is one of the main determinants of both Aδ and C LEPs.

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Clarifying methods of Truini et al. [Pain 2007;131:343–7] and proposing further evidence supporting the "first come first served" hypothesis: A reply to Mouraux and Iannetti

We are pleased to receive the comments by Mouraux and Iannetti. We appreciate their interest in our study and the scientific discussion they raise. In this reply, we shall first clarify some methodological points in our previous article that may have misled our colleagues, and will show that expectancy was indeed controlled for in our experiment. Then, we will make a case that, even if expectancy had been left uncontrolled, its effects on LEPs could not have been those that Mouraux and Iannetti (M&I) suppose. Finally, we shall provide further evidence that the mechanism tentatively labelled "first come first served" fulfils clear homeostatic functions in sensory integration.

We agree that expectancy may influence vertex potentials and plays some role in the modulation of LEPs. However, we believe that M&I's interpretation of our results originates from a misunderstanding of the Methods, admittedly due to some ambiguities in our description. We reported that in every block "*paired stimuli were pseudo-randomly alternated with occasional single stimuli (10–15 in total for each recovery curve), which served as control*". Mouraux and Iannetti inferred that we recorded only few controls per