Placebo Analgesia in Aging – the Impact of age-related cognitive decline

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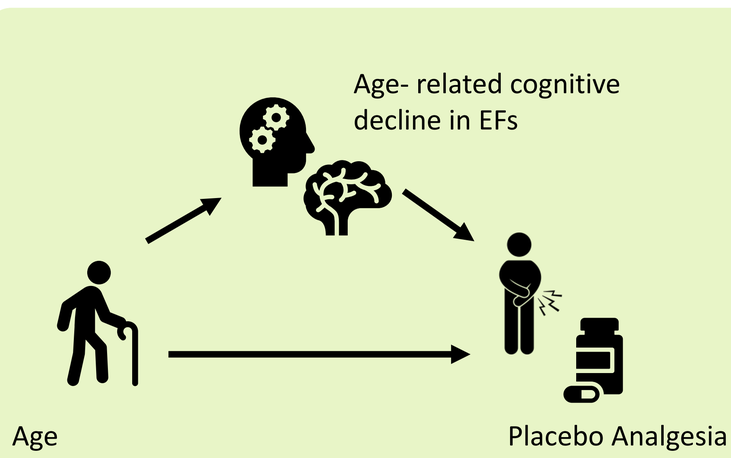
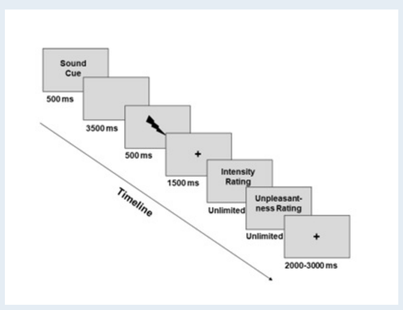
INTRODUCTION

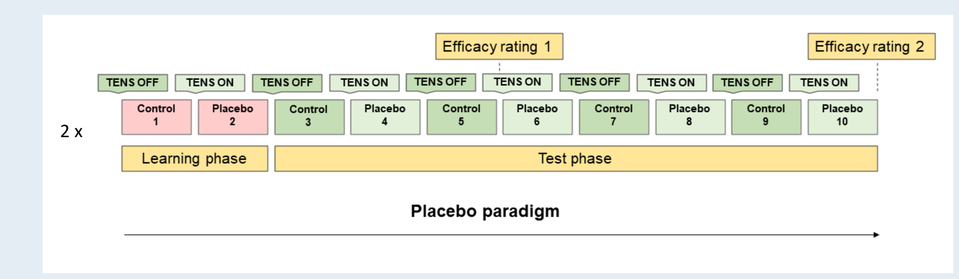
Placebo analgesia is a cognitive pain modulation mechanism with high relevance in pain treatment. Older people would benefit especially form it, since they are disproportionately affected by pain, while pharmacological treatments are less appropriate [1,2]. Although aging is known to affect physiological aspects of pain perception [3,4], the few studies on the effects on placebo analgesia revealed inconsistent results [5,6,7,8,9]. Executive functions (EFs), relying on PFC (prefrontal cortex) functioning, have been considered a key factor in the age – pain relationship [10], indicating age-related decline in EFs being associated with reduced placebo analgesia in older adults (OA).



Cognitive tasks:

1. Trail Making Test (TMT), digit span test, Go/NoGo task, Color Word Stroop test
2. executive control assessed with the Attentional Network Test (ANT)
3. Alerting assessed with the ANT





Material and Methods

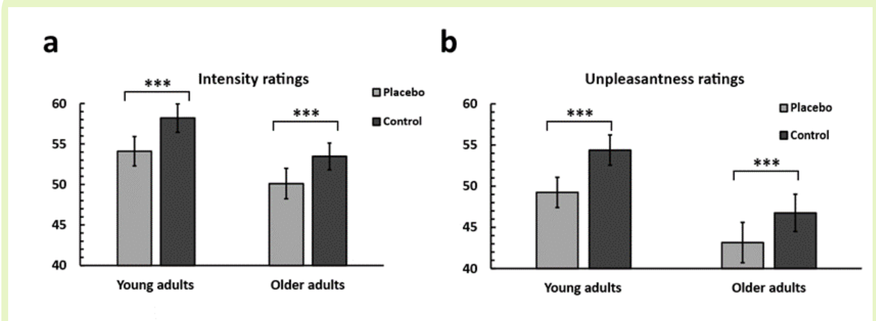
Placebo analgesia was assessed in 42 older (22 female; mean age = 67.80 (*SD* 5.70); 60-82 years) and 39 younger adults (22 females, mean age = 23.87 (*SD* 4.26); 18-36 years) via a sham trans-cutaneous electrical nerve stimulation (TENS) intervention, while participants received individually calibrated painful transcutaneous electrical stimuli to their inner forearm. In alternating blocks, participants were informed that the TENS device was switched ON or OFF while receiving unknowingly the same moderately painful stimulation. The sham TENS intervention involved verbal suggestions and a conditioning procedure, as well as reinforcement trials. Beforehand, participants completed several cognitive tasks, comprising EF tasks showing either age-related deficits (1) or not (2), as well as a non-EF task, showing age-related deficits (3). The extent of placebo-related pain relief according to subjective intensity and unpleasantness ratings was calculated and the N1-P2 ERPs of the electrical stimulation analyzed. Behavior results of the cognitive task were tested for their predictive value in the magnitude of the placebo analgesic effect.

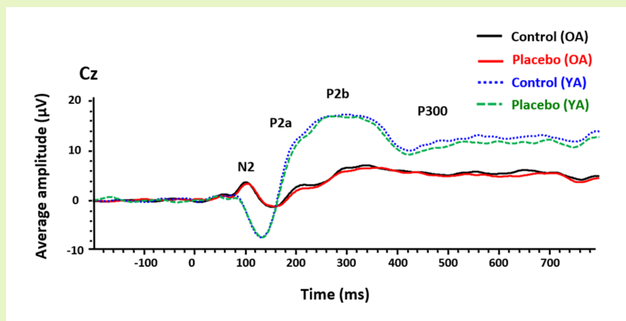
Results

We found preserved placebo analgesia in OA in respect to pain ratings and stimulus-locked ERPs of the EEG.

Importantly, age-related cognitive decline in **EFs** predicted the magnitude of the analgesic placebo effect. OA with worse performance in the TMT and digital span task showed a **reduced placebo-induced pain relief.**

In contrast, performance in EF tasks with **no** age impact or worse performance in **non - EF** (ANT alerting) were unrelated to the placebo analgesic effect in OA.





	B	*SE*	*p*	BCa 95% CI Lower	Upper
Constant	-7.33	5.36	.160	-18.746	1.856
Stroop effect	0.25	0.15	.111	-0.028	0.611
Digit span (sequential)	1.05	0.41	.020	0.312	1.832
TMT difference score	-0.07	0.03	.015	-0.142	0.039

Tabl. 1: Older adults: Regression model for the placebo effect with EFs showing age - related differences as predictors.

	B	*SE*	*p*	BCa 95% CI Lower	Upper
Constant	3.12	0.77	.001	1.736	4.804
Alerting effect	0.21	1.31	.874	-2.666	2.160
Executive control	1.39	0.80	.084	-0.063	3.003
Commission errors from the go/nogo task (controlled for time) [a]	-12.11	7.65	.095	-26.528	7.745

Tabl. 2: Older adults: Regression model for the placebo effect with EFs showing no age - related differences or non-EF cognitive function with an age-related decline as predictors.

Conclusion

Our results suggest that executive functions explain a significant portion of variance in older individuals' responses to a sham pain treatment/ the magnitude of the analgesic placebo effect. This finding may explain previous conflicting reports on age-related changes in placebo analgesia and highlights the importance of assessing, and controlling for, differences in executive functions. Moreover, individual cognitive trainings might enable older patients to benefit more from placebo effect as part of any treatment or drug.

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ACKNOWLEDGEMENT

The study was supported by the Luxembourg National Research Fund (FNR, C16/BM/11266318/ACHE).

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