

Effects of Donepezil on attentional processing and TMS measures of GABAergic and Cholinergic signalling

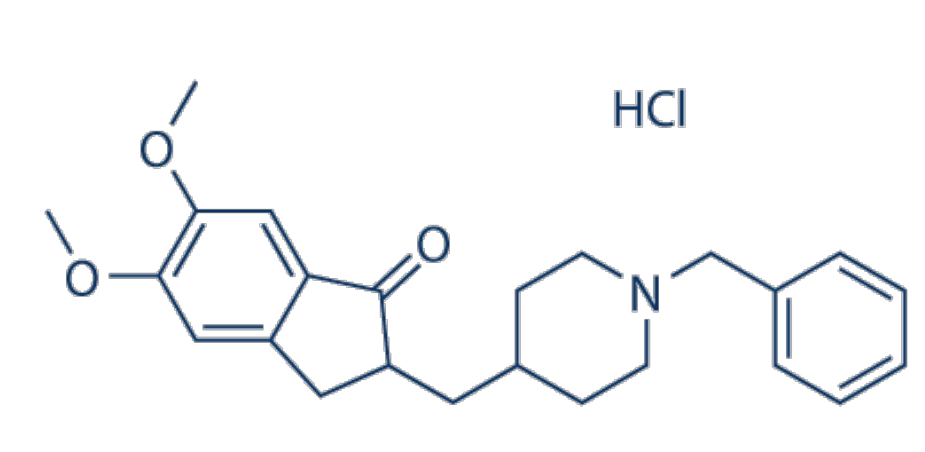
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Introduction

Many neurodegenerative diseases feature **cognitive impairments** coupled with **deficit** in **cholinergic** and **GABAergic** signalling. Indeed, Donepezil, a widely-used treatment for Alzheimer's Disease, works by extending the life of synaptic acetylcholine. This is believed to support cognitive functions; however, how this is achieved in the brain is poorly understood due to scarce neuroimaging evidence.

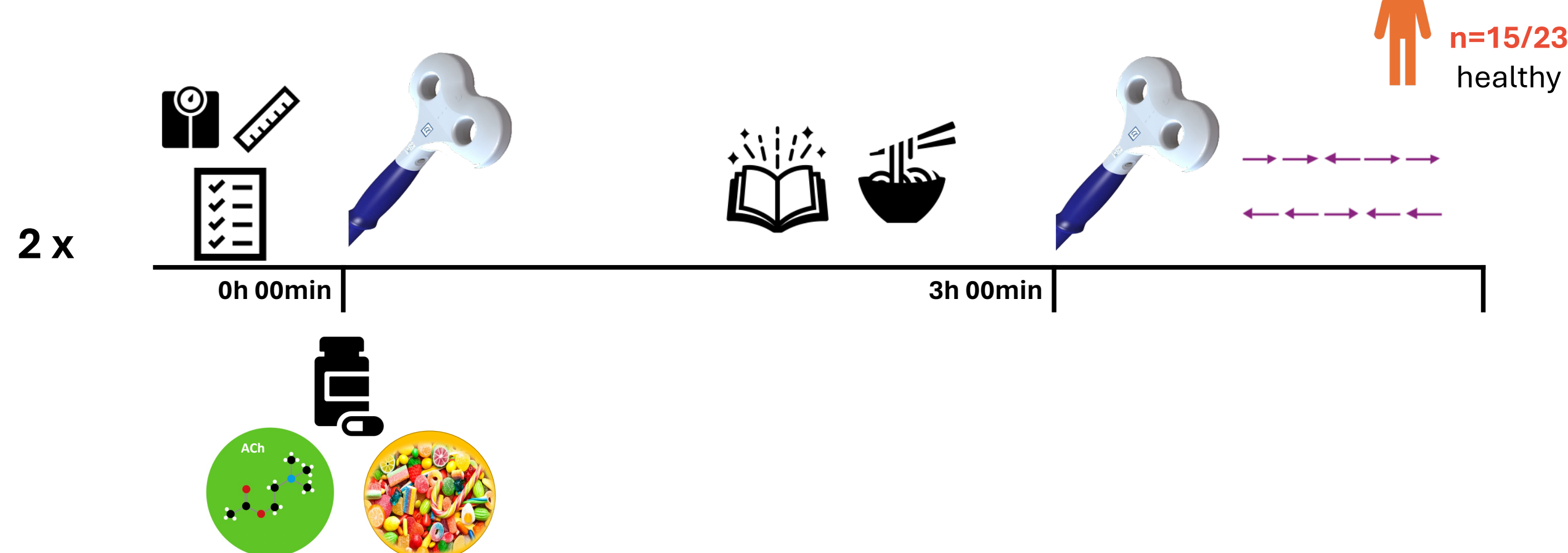
Cholinergic signalling is believed to underlie **orienting attention**, i.e., directing our attention to a stimulus, while **GABAergic** signalling is thought to be involved in **executive control**, i.e., resolving conflicting information.



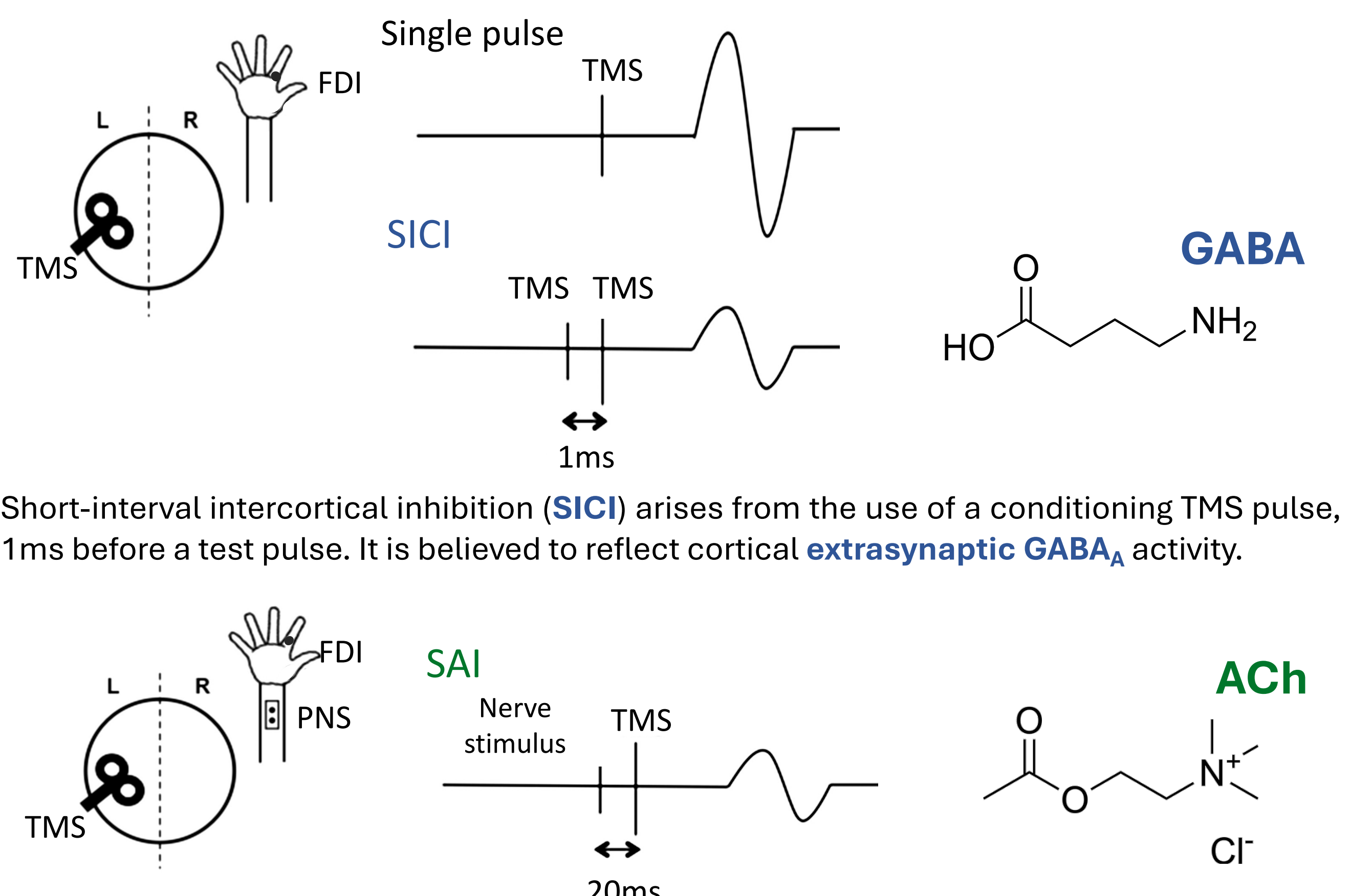
Here, we assessed the effects of **pro-cholinergic** drug Donepezil on measures of **attentional processing** and **TMS measures of cortical excitability** in healthy adults. Our work elucidates the effects of a commonly prescribed drug, which may explain its variable efficacy and improve its future clinical use.

Methodology

Study design



SICI and SAI – measures of GABA and ACh?

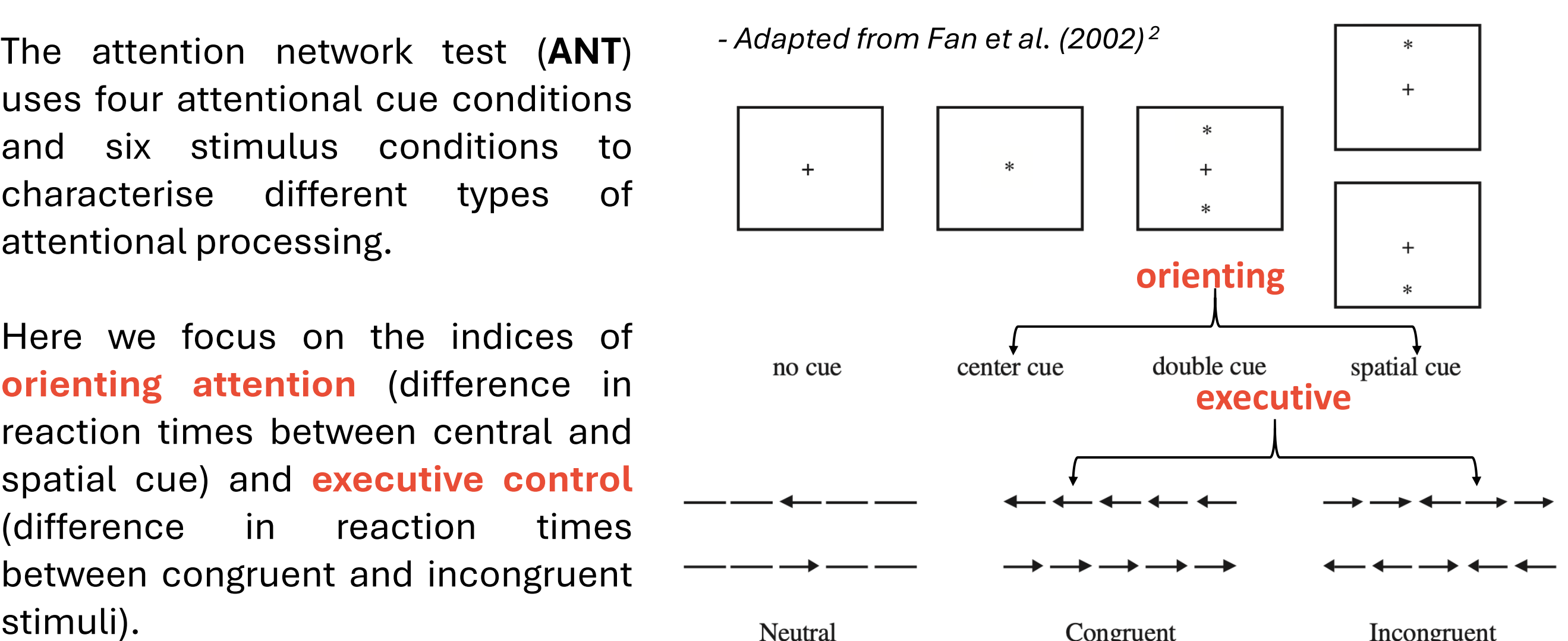


Short-interval intercortical inhibition (**SICI**) arises from the use of a conditioning TMS pulse, 1ms before a test pulse. It is believed to reflect cortical **extrasynaptic GABA_A** activity.

Short-latency afferent inhibition (**SAI**) arises from the use of a conditioning peripheral stimulus, 20ms before a TMS pulse. It is believed to reflect **thalamocortical cholinergic** signalling.

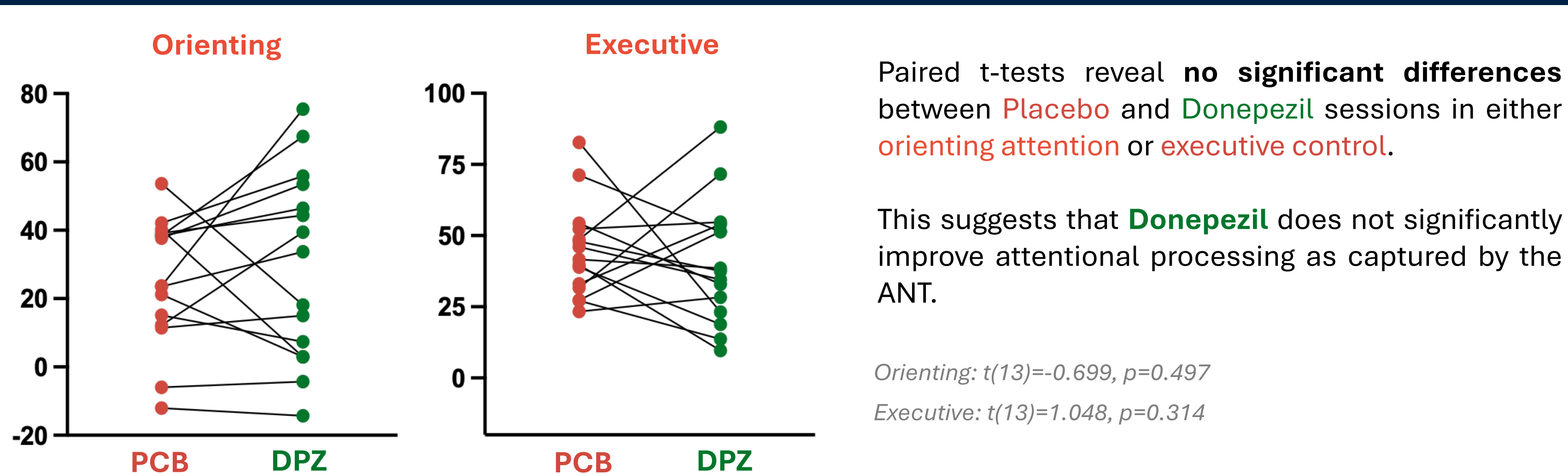
- Adapted from Turco et al. (2018)¹

ANT – a behavioural measure of attention

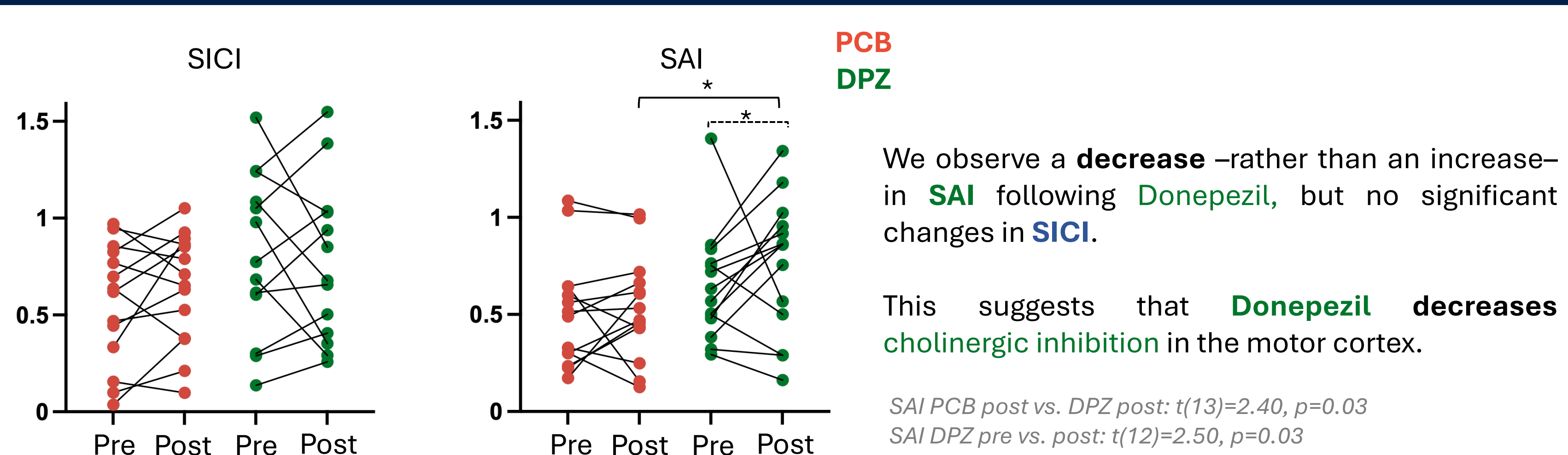


Here we focus on the indices of **orienting attention** (difference in reaction times between central and spatial cue) and **executive control** (difference in reaction times between congruent and incongruent stimuli).

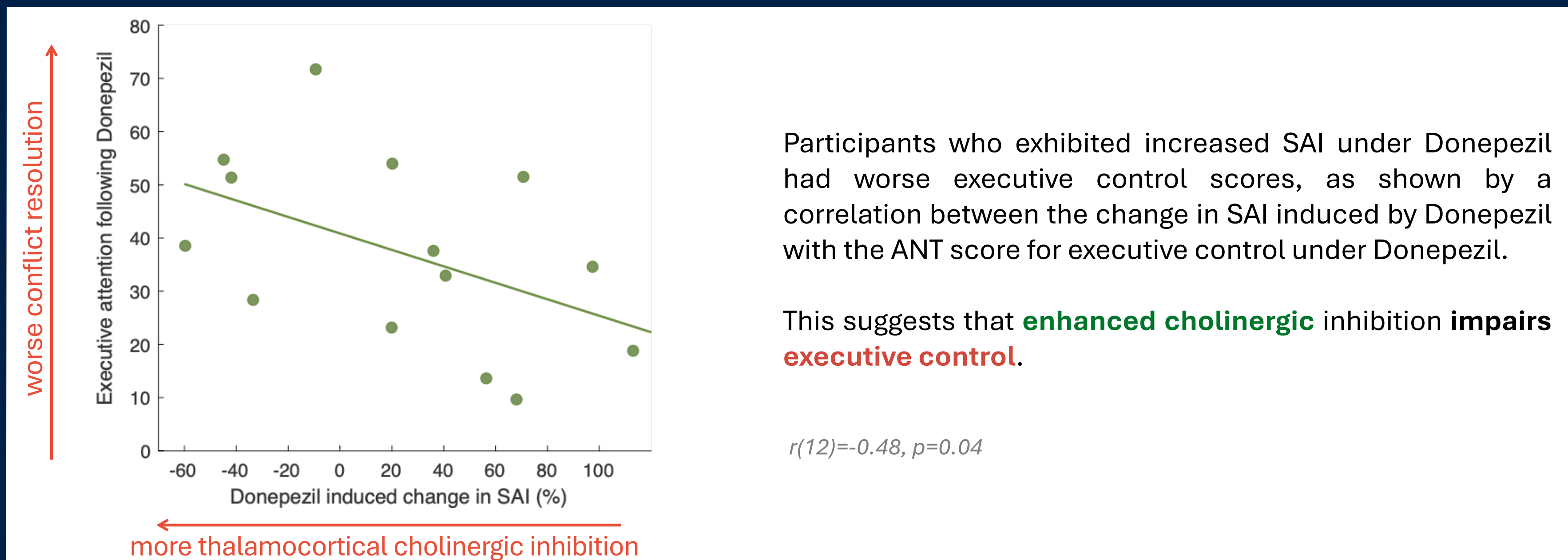
Donepezil does not impact attentional processing



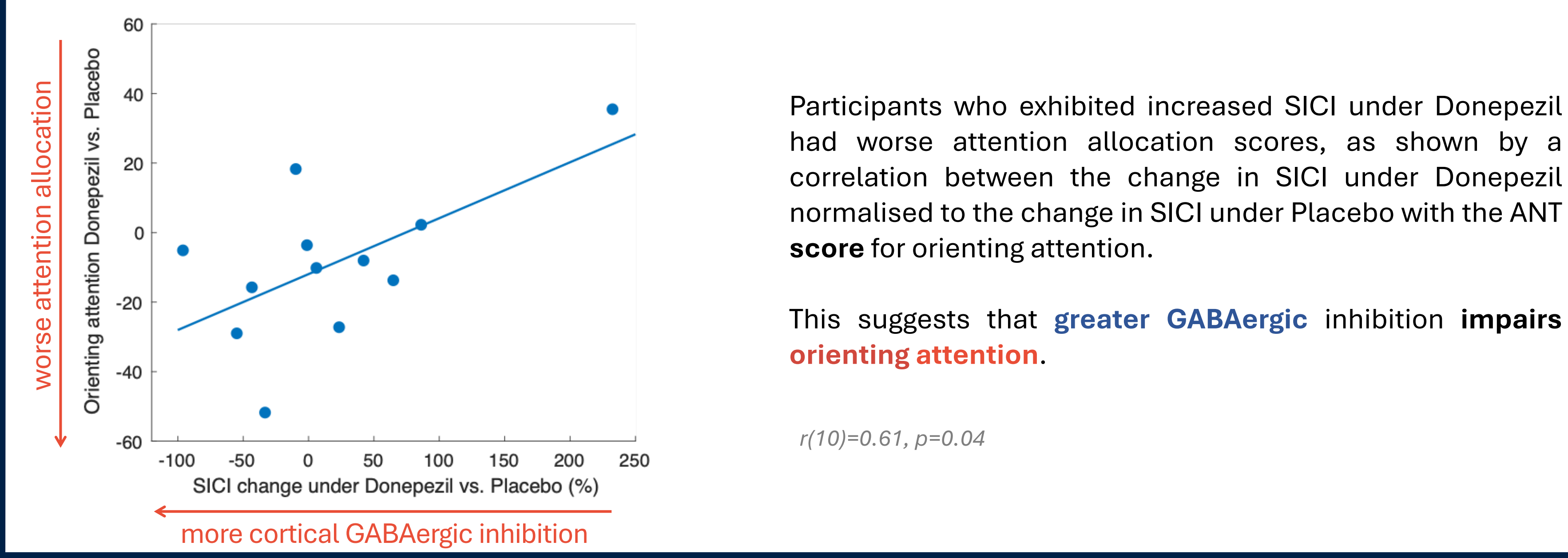
Donepezil decreases SAI?



Increased SAI impairs executive control

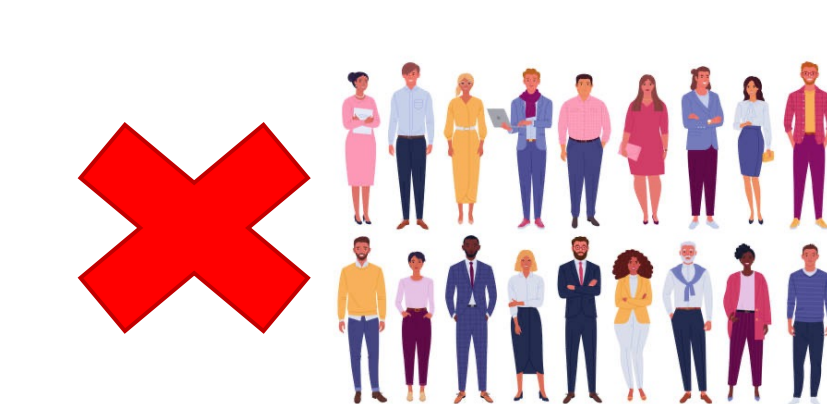


Increased SICI impairs orienting attention

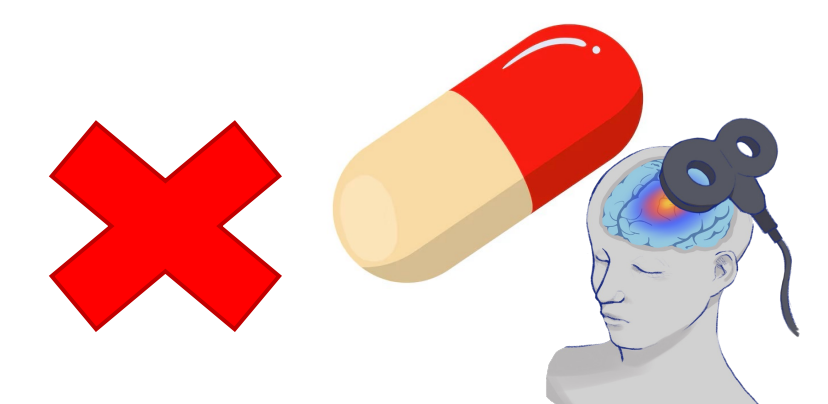


Conclusion & Future Work

Our **Donepezil-induced** findings are **inconsistent** with the **hypothesised** role for **cholinergic** and **GABAergic** signalling and **could explain** its **variable efficacy** and inform its use.



Results are **preliminary** – power analysis suggests **23 participants required**. Greater (on-going) **recruitment is necessary**.



Drug **dosage/regimen** and **indirect** measurement may have impacted results.



Direct-measurement of cholinergic changes (e.g., MRS) or **alternative interventions** to enhance cholinergic activity (e.g., TUS) should be explored.

References

¹Turco, C. V. et al. Short- and long-latency afferent inhibition; uses, mechanisms and influencing factors. *Brain Stimulation* **11**, 59–74 (2018).
²Fan, J. et al. Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience* **14**(3), 340–347 (2002).