WHY DO AMYLOID TRIALS FAIL? SIMULATING THE IMPACT OF AMYLOID MODULATION INTERVENTIONS IN A MECHANISM-BASED COMPUTER MODEL OF ALZHEIMER'S DISEASE

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Background

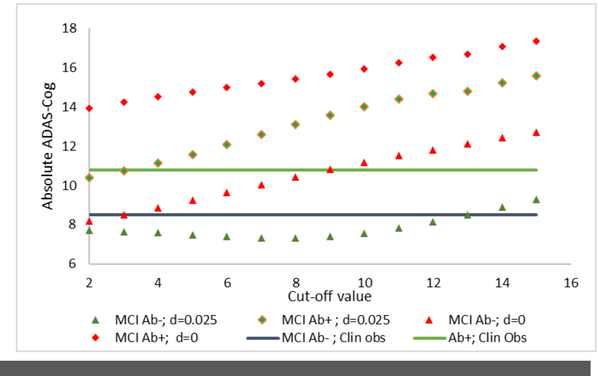
Aβ1-40 and Aβ1-42 oligomers have complex effects on excitation-inhibition balance. Low Aβ40 levels improve, but high Aβ1-40 levels reduce Glu transmission. Aβ1-42 reduces Glu transmission at all doses (Wang 2013). Aβ1-40 and Aβ1-42 reduce alpha7 nAChR.

These non-linear effects are implemented in an ADAS-Cog calibrated Quantitative Systems Pharmacology neuronal network computer model.

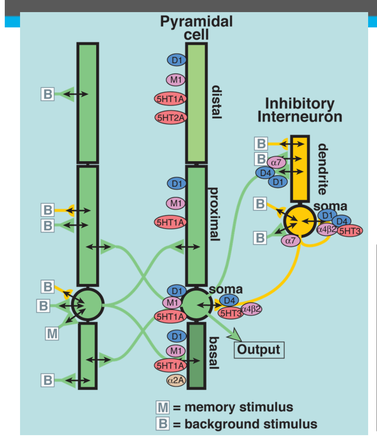
Model is constrained by clinical observations on (1) absolute ADAS-Cog values in Aβ- and Aβ+ MCI subjects (Doraiswamy 2014), (2) the differential impact of Aβ on the dose-response of scopolamine in MCI patients (Lim 2015) and (3) the absence of effect of APOE on the cognitive trajectory in unmedicated AD patients (Samtani 2016)

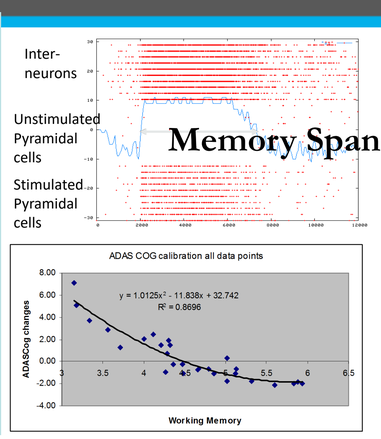
Absolute ADAS-Cog values for MCI

Absolute ADAS-Cog predictions in an MCI 'virtual patient' for different cut-off values for Aβ+ and Aβ- imaging SUVR values. For the optimal parameter set for δ=0.025, α, α* and β (x_0 fixed at 2) values for Aβ- and Aβ+ MCI subjects is shown by the blue points and the green points., with predicted values are near the clinical values at a cut-of value of 3. For δ=0 the average ADAS-Cog prediction for Aβ- and Aβ+ patients is shown by the red points and orange points. This suggests that the condition where δ=0, (no beneficial effect of Aβ40) is unable to reproduce this clinical outcome



Quantitative Systems Pharmacology Model





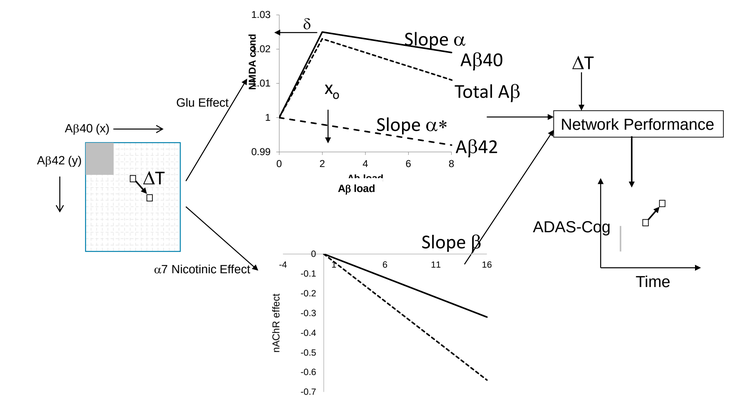
(Left) Representation of the cortical cognitive model for Alzheimer's disease. The membrane potential modulated by the effect of GPCR on the conductance of voltage gated ion-channels is calculated at a time resolution of 0.050 msec. AD pathology is introduced as a lower cholinergic tone and a gradual loss of synapses and neurons over time. (Right Top) The network (80 pyramidal neurons and 40 interneurons) simulates the time that a memory representation can be held in the network without further stimulation, which is a proxy for working memory performance. (Right Bottom) We calibrated the biological parameters with historical data on 28 different drug-dose combinations on ADAS-Cog changes. The correlation between model outcome (positive is worse) and the clinical results suggest that the model captures a substantial amount of variance (Roberts 2012).

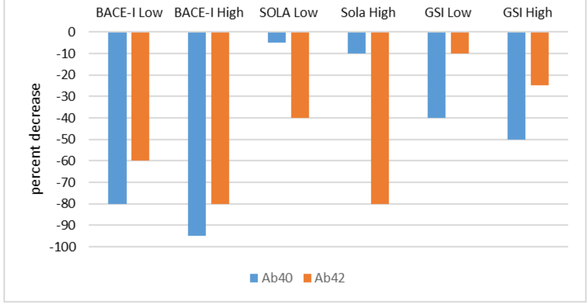
Sensitivity Analysis on clinical observations

	δ=0			δ=0.01			δ=0.02			δ=0.025			δ=0.03			δ=0.04		
α+α*	β=0.01	β=0.02	β=0.03	β=0.01	β=0.02	β=0.03	β=0.01	β=0.02	β=0.03	β=0.01	β=0.02	β=0.03	β=0.01	β=0.02	β=0.03	β=0.01	β=0.02	β=0.03
0.0002	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2	0	0	0
0.0011	0	0	0	0	0	0	2	2	2	2	2	2	0	2	2	0	0	0
0.001	3	3	3	3	3	3	2	2	2	2	2	2	2	2	2	0	0	0
0.002	0	0	0	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2
0.003	0	0	0	0	0	0	123	123	123	12	12	123	23	23	23	2	2	2
0.004	0	0	0	0	0	0	23	23	23	123	123	123	123	123	123	23	23	23
0.005	0	0	0	0	0	0	2	2	2	23	23	23	123	23	23	23	123	123

Systematic sensitivity analysis of model outcome for all key parameters of the model with value for x_0 fixed at 2. Each cell lists which of the following conditions are met. (1) Absolute ADAS-Cog in MCI Aβ− and MCI Aβ+ patients, (2) greater sensitivity to scopolamine in MCI Aβ+ subjects, (3) Difference of maximal 10% between cognitive trajectory slopes for APOE4+/+, APOE4+/- and APOE4 -/- with APOE4+/+ genotype at least 1.5 point worse than the APOE4-/- . Only for some conditions δ>0.02 and (α+α*)>0.003 all three conditions are met simultaneously. In the δ=0 case (i.e. no protective effect of the short Aβ form), no case exists where all three conditions are met simultaneously

Relating Abeta to Cognitive Readout

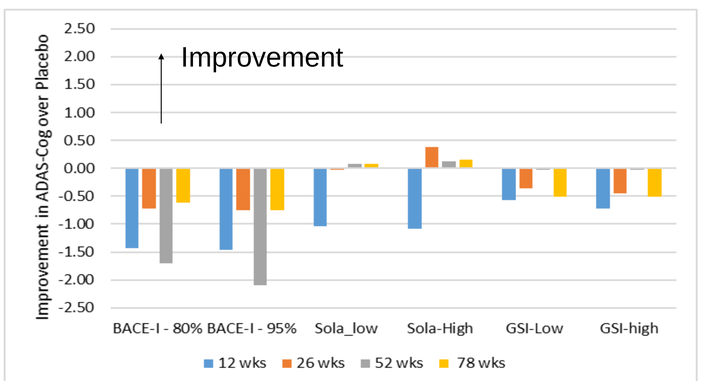


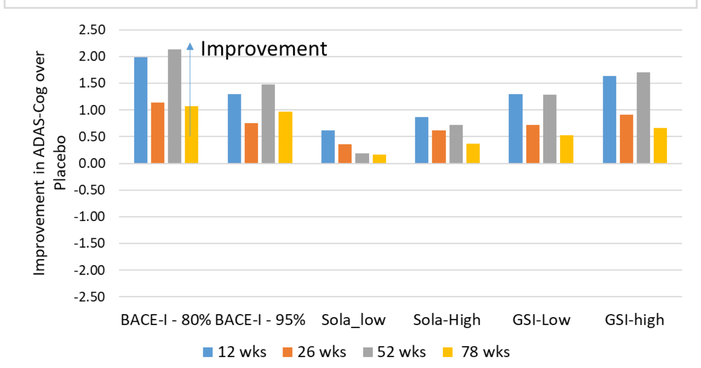


Changes in soluble Abeta forms in clinical trials after treatment with the BACE inhibitor (Van Maanen 2016), the monomer antibody solaneuzumab (Farlow 2012) and the Gamma-secretase inhibitor semagacestat (Doody 2015).

Modeling pipeline for simulating the effect of changes in Aβ40 and Aβ42 concentrations on cognitive outcome. Each value of Aβ40 and Aβ42 oligomers (left matrix), changes excitatory-excitatory (e-e) NMDA conductance and a7 nAChR activation as derived from the coupling equations and the outcome on a cognitive neuronal network is calculated. (Top) Relationship between Aβ40 and Aβ42 load and e-e NMDA conductance with maximum value δ at position x_0 and slopes α, α*. (Bottom) Relationship between Aβ load and α7 nAChR inactivation with slope β. The cognitive outcome matrix for a baseline value and for six different disease states. The Aβ load (left matrix) of an AD patient can be defined for any region and its cognitive status can be determined by averaging the range of results at a particular time (the gray line in the right graph). Similarly, for any change in Aβ40 and Aβ42 oliogmers as a consequence of disease pathology or therapeutic interventions over a time span of ΔT, the corresponding changes in ADAS-Cog can be calculated based on their impact on cognitive readout changes using their Glutamate and α7 nAChR mediated effects.

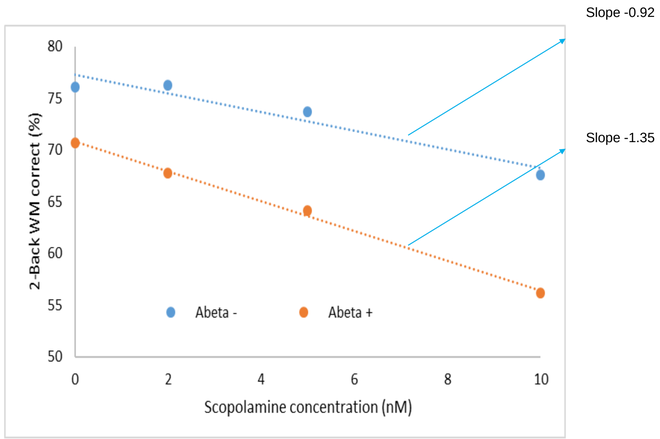
Therapeutic Interventions





Simulated differences with placebo values in ADAS-Cog scale in a 78-week trial with mild-to-moderate AD patients with a low or zero amyloid baseline (top) and high amyloid (bottom) after BACE inhibition (verubecestat), gamma-secretase inhibition GSI (semagecestat) and solanezumab antibody. All interventions worsen cognition in the low amyloid case, while in the high amyloid case, BACE-I improves cognition, (maximal 1-2 points), and GSI has a smaller dose-dependent response (1-1.5 points). Solanezumab on the other hand has only a modest dose-dependent clinical benefit (0.5-1 points).

Recapitulation of Clinical Observations



Dose-response of scopolamine mediated cognitive deficits in a MCI population with and without Aβ amyloid load for δ = 0.25 and α=0.00175 as measured in the 2-back working memory test. The slopes for the Aβ- and Aβ+ condition are -0.92 and -1.35 % correct responses/nM scopolamine, respectively with higher Aβ load making the system more sensitive to scopolamine. The pharmacodynamical interaction between cholinergic neurotransmission and Aβ can have important consequences in clinical trials.

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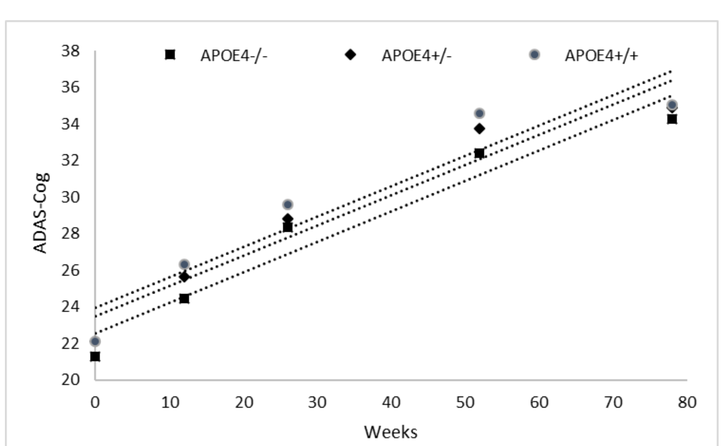

Simulated outcome of APOE genotype on changes in ADAS-Cog between 0 and 78 weeks for placebo patients with Aβ starting load (above the cut-off threshold for imaging). APOE4+/+ genotype is implemented in the QSP platform as having lower synaptic density (-20%) and lower clearance of Aβ isoforms (-25%). Because the slopes are parallel, the platform outcome suggests that under these conditions APOE does not affect disease progression as shown in the placebo arm of the bapineuzumab trail (Samtani 2016).

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Conclusion

- Only when assuming a neurostimulatory effect of short Aβ forms can the QSP model correctly reproduce 3 clinical outcomes sets.
- The effect of GSI and BACE-I is dependent upon Aβ load; monomer vaccination is much less sensitive. They only improve cognition in situations with high amyloid load. The non-monotonic dose-response is dependent upon the baseline Aβ load
- Higher effect of therapeutic interventions at high Aβ load might explain greater effectiveness in Tg animals models with artificially high amyloid levels
- Most importantly, for low Aβ oligomeric loads, BACE-I and GSI and to a lesser extent solanezumab ***worsen cognitive outcome***.
- ***These results questions the rationale to test amyloid therapies in pre-symptomatic low amyloid healthy elderly "before the amyloid pathology starts"***.
- Model predictions can be confirmed by post-hoc analysis of individual patients in failed amyloid trials.
- Limitations
  - Impact of oligomeric beta-amyloid on neurotoxicity is ignored
  - Only two physiological processes implemented

References

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