Title: Attentional deficits in Alzheimer's disease: investigating the role of acetylcholine with computational modelling

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Introduction

Attention is a very important cognitive process that is employed for many actions in our everyday life (e.g. watching television, reading a paper, washing our face, eating and so on). It is therefore essential to investigate further the underlying mechanisms in neuro-degenerative conditions, like Alzheimer's disease, in which our attentional abilities are reduced (Festa, Heindel, & Ott, 2010; Foster, Behrmann, & Stuss, 1999; Hao et al., 2005; Porter, Tales, et al., 2010; Redel et al., 2012; A. Tales et al., 2002a; Vallejo et al., 2016). Alzheimer's disease is a condition that can take several years if not decades from the time it starts to the time the full symptoms are shown (Tijms & Visser, 2018). In those years of disease progression, there are a number of pathological processes that are taking place, however one of the starting point of the pathology is believed to be the aggregation of β amyloids into plaques (Gordon et al., 2018; Tijms & Visser, 2018). Irrespective of the amount of research that has taken place, many questions remain on how the disease unfolds and how to identify individual's position in the disease's trajectory (Gordon et al., 2018; Ryman et al., 2014).

It is therefore essential to fully understanding the underlying processing and progression mechanisms of the pathology. Understanding the progression of the pathology will allow for early diagnosis, and improve medications and managements providing better and longer life for patients. In fact to achieve this, it has been argued that cognitive tasks related to cognitive impairments are reliable measures to predict progression of the disease (Belleville, Fouquet, Hudon, Zomahoun, & Croteau, 2017). As previously discussed, one of the cognitive functions that is affected in Alzheimer's disease is attention (Festa et al., 2010; Foster et al., 1999; Hao et al., 2005; Porter, Tales, et al., 2010; Redel et al., 2012; A. Tales et al., 2002a; Vallejo et al., 2016). Patients with Alzheimer's disease have been shown to have reduced visual processing and attentional orienting (Li et al., 2015) that affect their attentional processing and visual search (Corbetta, Patel, & Shulman, 2008; Li et al., 2015).

To investigate further attentional processing, researchers have been using the single feature and conjunction search tasks (Moran et al., 2016; Redel et al., 2012; Watson & Humphreys, 1997; Wolfe, 2002). In both experiments, subjects are asked to identify a target amongst distractors. In single feature search, the target shares one common feature with distractors, for example a target blue *H* amongst blue *A* distractors. In the conjunction task, the target shares two different features with the distractors, for example a target blue *H* amongst distractors that are blue *As* and green *Hs* (Watson & Humphreys, 1997; Wolfe, 2002). Patients with Alzheimer's disease show reduced activation in visual, dorsal attention and ventral attention networks (Li et al., 2015) leading to expected deficits in attentional processes (Festa et al., 2010; Foster et al., 1999; Hao et al., 2005; Porter, Tales, et al., 2010; Redel et al., 2012; A. Tales et al., 2002a; Vallejo et al., 2016). Interestingly, the patients show a significant decrease in performance in the difficult conjunction task but no significant changes in the easy single feature search (Cormack, Gray, Ballard, & Tovée, 2004; Foster et al., 1999; Hao et al., 2005; Porter, Leonards, et al., 2010; A. Tales et al., 2002b; Andrea Tales & Porter, 2008). Researchers suggest

that this might be due to an impairment in the binding and grouping processes (Hao et al., 2005), problems with inhibitory processes (Levinoff, Li, Murtha, & Chertkow, 2004; Parasuraman, Greenwood, & Alexander, 2000) or due to acetylcholine changes that are linked to Alzheimer's disease (Bertrand & Jr, 2018; Daiello et al., 2010; Levy, Parasuraman, Greenwood, Dukoff, & Sunderland, 2000; Mesulam, 2004; Sultzer et al., 2017; Whitehouse et al., 1986).Acetylcholine is directly linked to attentional processes (Gustavo Deco & Thiele, 2009; Hedrick & Waters, 2018; Levy et al., 2000; Sparks, Proulx, Lambe, Barrett, & Chattarji, 2018), through its cholinergic projections from the basal forebrain (Hedrick & Waters, 2018). Pyramidal neurons modulated by Acetylcholine express nicotinic and muscarinic receptors (Hedrick & Waters, 2018). Acetylcholine modulation from the nucleus basalis magnocellularis is linked to changes in binding in visual search tasks (Botly & De Rosa, 2012) and changes in feature binding affect the difficult rather than easy visual search (Treisman & Gelade, 1980). Furthermore, acetylcholine modulation affects attentional processes through gamma synchrony (Gustavo Deco & Thiele, 2009), which is linked with changes observed in oscillatory activity in Alzheimer's disease. In fact, Deco and Thiele (2009) identified that there is an optimum ratio between NMDA and AMPA conductance that is linked to acetylcholine, gamma oscillations and optimum attention.

All cognitive processes rely on rapidly occurring coordinated action among distributed neural assemblies. Thus, one approach to understand and identify when and how these processes go wrong is to measure coordinated neural activity in brain networks. Neural oscillations, as observed with EEG or MEG (M/EEG), are such a measure. Brain oscillations represent regular fluctuations in electrical potentials/magnetic fields and are generated by tens of thousands of neurons. Oscillations occur at different frequencies, ranging from very slow (0.2 Hz) to very fast (300 Hz), where the frequency of an oscillation is thought to inversely reflect the size of the network generating the oscillation. Brain oscillations thus capture the fundamental characteristics of the structural wiring of the brain, and allow neural communication during different cognitive states (rest, perception, memory, etc.) to be explored at the temporal resolution at which neurons operate. For this reason, brain oscillations are a promising candidate for charting neurological and psychiatric disorders (Colom, García-Hernández, Castañeda, Perez-Cordova, & Garrido-Sanabria, 2006; Gallego-Jutglà, Solé-Casals, Vialatte, Dauwels, & Cichocki, 2014; Güntekin, 2008; Reiterer, Pereda, & Bhattacharya, 2011; Zamrini et al., 2011).

There is an expanding literature on MEG/EEG (M/EEG) correlates of a range of disorders, such as, epilepsy, memory impairments, OCD and ADHD (Güntekin, 2008). Of particular relevance, there are now a number of findings on oscillatory correlates of Mild Cognitive Impairment (MCI), e.g. (Gomez, Stam, Hornero, Fernandez, & Maestu, 2009); Alzheimer's, e.g. (Stam, Jones, Nolte, Breakspear, & Scheltens, 2006) and other dementias, e.g. (Hughes & Rowe, 2013); including in large multi-site studies (Maestú et al., 2015).

Additionally, in the resting state brain (in which stationarity of oscillatory features can be assumed), a number of interesting findings have been reported. For example, one hallmark of dementia, particularly Alzheimer's, is a general slowing of the resting state frequency spectrum (Montez, Poil, …, & 2009, n.d.). Additionally, Poil et al. (2013) found a wide spectrum of EEG resting state measures that predicted progression to Alzheimer's, with a broader beta power peak most predictive (Poil et al., 2013).

The oscillatory correlates of MCI are perhaps particularly important for attention as well, since it is frequently a precursor diagnosis to Alzheimer's. As a result, its detection is a target for work on biomarkers of the very early stages of Alzheimer's. With this goal in mind, an oscillatory EEG pattern that distinguishes Mild Cognitive Impairment (MCI) patients who either progress within 3 years (convertors) or do not (stable) to Alzheimer's Disease (AD) has been identified (Mazaheri et al., 2018).

Figure 1 shows time-frequency spectra for brain activity arising from lexical processing. Importantly, healthy controls (panel [1]) and non-progressors (i.e. MCI-stable, panel [2]) show a clear increase in theta power 0 to 0.5s after word onset (warm colours), while MCI-convertors (panel [3]) show a reduced increase (convertors<stable: $p<0.046$; convertors<control: $p<0.004$). Such an oscillatory change for lexical processing is consistent with language deficits in AD (Ferris & Farlow, 2013) .

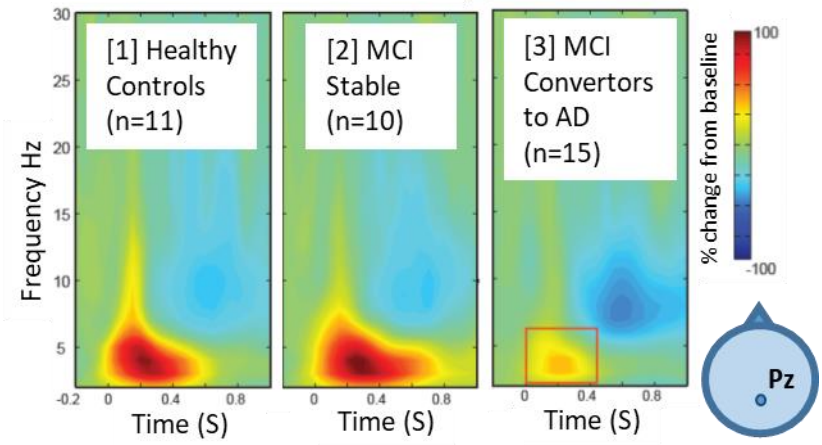

Figure 1: An attenuation of theta activity associated with lexical processing in a group of MCI patients who would go on to convert to Alzheimer's disease (Mazaheri et al., 2018). The time-frequency spectra are locked to word onset at the midline-parieta

A key question that follows is the effect of neuromodulators on these EEG patterns. As previously discussed, there is considerable evidence that there are a range of changes to neuromodulators associated with the development of dementias. In this respect, changes in Acetylcholine are of particular interest. There are, though, few studies that explicitly consider differences in human EEG features between groups with and without Alzheimer's when Acetylcholine is manipulated.

One of the few studies that explicitly targeted this question is by Yener and collaborators (Yener, Güntekin, Öniz, & Başar, 2007). They compared Healthy Controls with Alzheimer's patients on and off AchEI, a compound that increases the level and duration of action of Acetylcholine. The authors found a reduction in phase-locking (to stimulus presentation) of theta oscillations at a frontal electrode for the Alzheimer's group that were not on AchEI, i.e. who, it is assumed, had depleted Acetylcholine. It is notable that theta was the relevant oscillation both in the Yener et al. (2007) and the Mazaheri et al. (2018) studies. This said, the former focussed on phase coherence across replications, while the latter focussed on power changes, and electrode sites were different. Nonetheless, the link between depleted Acetylcholine in Alzheimer's and a noisier stimulus locked theta oscillation is definitely worth further exploration.

An attractive way to proceed in this line of research is computational modelling, which allows data collected from all different methodologies to be combined, to test outcomes and to provide predictions for further testing (Alexiou, Mantzavinos, & Greig, 2017; Gustavo Deco & Thiele, 2009; Li et al., 2015; Eirini Mavritsaki, Heinke, Allen, Deco, & Humphreys, 2011; Eirini Mavritsaki & Humphreys, 2016). It is very important therefore to use computational modelling to help us interpret the findings so far and to progress further. Moreover, developed computational models could then be used to predict the progression of the disease on an individual basis, and predict the efficacy of different drug

targets in Alzheimer's disease if the model captures the mechanism of these drug compounds in the patients. If the model parameters can be determined at individual rather than group level, such model paves the way for personalized treatments.

Accordingly, researchers have started modelling Alzheimer's disease (Alexiou et al., 2017; Yu & Dayan, 2002; Adeli, Ghosh-Dastidar, & Dadmehr, 2005), but they have focused on low level properties of the system, rather than linking neurophysiological damage with behaviour. In contrast, in the work presented here, we use a computational model that can allow these two levels to be linked and allow us not only to understand Alzheimer's at the neuronal level but also how changes observed in Alzheimer's disease are linked with behavioural changes. The selected behavioural study is visual search, this is because, as previously discussed, there is a good deal of work in the area that identifies depletion in attentional processes in Alzheimer's disease and links it to acetylcholine function, and attention deficit underlies many cognitive dysfunctions in Alzheimer's disease (Gustavo Deco & Thiele, 2009; Festa et al., 2010; Foster et al., 1999; Hao et al., 2005; Porter, Tales, et al., 2010; Redel et al., 2012; A. Tales et al., 2002a; Vallejo et al., 2016). Furthermore, this work is based on the binding spiking Search over Time and Space (bsSoTS) (Eirini Mavritsaki & Humphreys, 2016) that has been extensively used to simulate visual attention processes in healthy adults (E. Mavritsaki, Heinke, Humphreys, & Deco, 2006; Eirini Mavritsaki, Allen, & Humphreys, 2010a; Eirini Mavritsaki et al., 2011) and to investigate further the attentional processes in conditions where such processes are depleted (Eirini Mavritsaki, Allen, & Humphreys, 2010b; Eirini Mavritsaki et al., 2011; Eirini Mavritsaki & Humphreys, 2016). The bsSoTS is also the appropriate model to use because the parameters of the model have been set to generate neural activity resembling that of the human brain in the content of realistic noise component. To simulate the acetylcholine depletion the work of Deco and Thiele (2009) is followed where the attentional behaviour changes are investigated by changes in acetylcholine levels through the AMPA and NMDA currents.

Methods

The methodology presented in this work is based on the bsSoTS model that uses integrate-and-fire neurons to simulate the traditionally used visual search experiment (Eirini Mavritsaki et al., 2011; Eirini Mavritsaki & Humphreys, 2016). Neuronal properties are described in Mavritsaki et al. (2016) based on the integrate-and-fire neurons of Brunel and Wang (2001). Input to the cell is based on a fast excitatory AMPA current, a slow excitatory NMDA current, a inhibitory GABA current and frequency adaptation based on the calcium sensitive potassium current I_{AHP}. The model is ideal for this level of simulations as it has successfully simulated the easy and difficult visual search experiment and incorporates top-down and bottom-up processes (Eirini Mavritsaki et al., 2011; Eirini Mavritsaki & Humphreys, 2016), as well as allowing us to investigate neuronal changes dependent on the AMPA, GABA and NMDA currents (Eirini Mavritsaki & Humphreys, 2013). The organisation of the model is based on previous work by Deco and Zihl (2001) and follows Feature Integration theory (Treisman & Gelade, 1980). The model simulates visual search experiments as described above. The general organisation of the model and the spiking and mean-field neuronal level is presented in Figure 2; to model the simulated experiment the model is divided into three layers: two feature layers whose activation is bound into the Location Map/Saliency Map (Eirini Mavritsaki et al., 2010a). Each Feature dimension layer is separated into two feature maps: the shape feature layer is separated into *H* and *A* and the colour feature layer is separated into colour blue and colour green, as in previous work (E. Mavritsaki, Heinke, Allen, Deco, & Humphreys, 2011; Eirini Mavritsaki & Humphreys, 2016, 2013).

Following the work by Deco and Thiele on the effects of acetylcholine on attention (Gustavo Deco & Thiele, 2009), we investigated the effects of changes in g_{NMDA} and g_{AMPA} on attentional processes in an effort to simulate the changes in visual search, assuming only changes in Acetylcholine. We changed the AMPA and NMDA conductance from performance observed in Alzheimer's -16% to 16%. Figure 3 (gAMPA/gNMDA graph) presents the effect of the changed values to the ratio of the NMDA/AMPA conductance (Gustavo Deco & Thiele, 2009). Within this range of parameters, we identified the parameters that allow for a different decline in visual search performance to be observed for simulated Alzheimer's disease between difficult and easy conditions. From the range of parameters investigated, the parameter settings that allowed for a greater decline in performance for the difficult relative to single feature search task, was selected. The single feature and conjunction visual search experiments were simulated for this selected set of parameters.

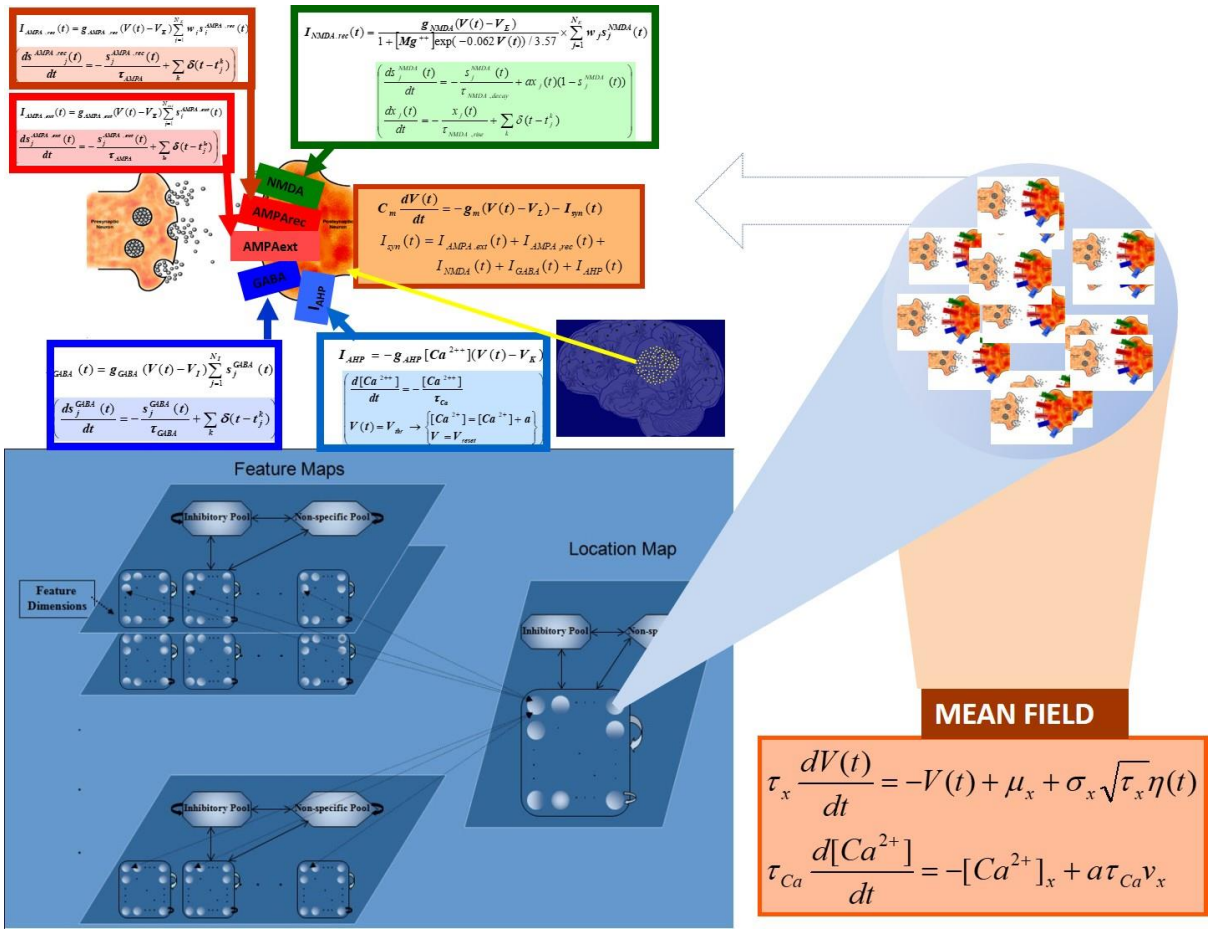

Figure 2: bsSoTS organisation for a range of feature maps. For the results presented in this work, we are using two feature maps for shape and colour. The model is overall separated into three layers, two layers for encoding the feature characteristics (the two feature maps) and a third layer in which all information is combined, the Location Map (Eirini Mavritsaki et al., 2010a). To constrain the model, we move through two different levels, level one is the Mean Field, where a group of neurons is simulated using a transfer function as shown in the Figure 2 and the spiking level, where each neuron is simulated using the equations shown on the top left corner of the figure. For more details on the model please see Mavritsaki and colleagues work (Eirini Mavritsaki et al., 2011; Eirini Mavritsaki, Heinke, Humphreys, & Deco, 2006; Eirini Mavritsaki & Humphreys, 2016).

The Poisson noise presented to the model allows us to simulate human performance by running the model for 300 trials for each display size (four and six) in single feature and conjunction conditions. This analysis follows the same analysis that was previously performed (Eirini Mavritsaki et al., 2011; Eirini Mavritsaki & Humphreys, 2016, 2013). The reaction times (RTs) and success rates obtained were then analysed using a mixed ANOVA design.

Results

The RTs and success rates for all the gNMDA and gAMPA parameter changes presented in Figure 3 are calculated for each parameter set and presented in Figures 3 and 4. The changes for RTs and success rates for single feature were smaller than the changes for conjunction. The circled parameter set identified in Figures 3 and 4 is the one selected to simulate the Alzheimer's condition. Figure 5 illustrates the average RTs and Figure 6 illustrates the average success rates.

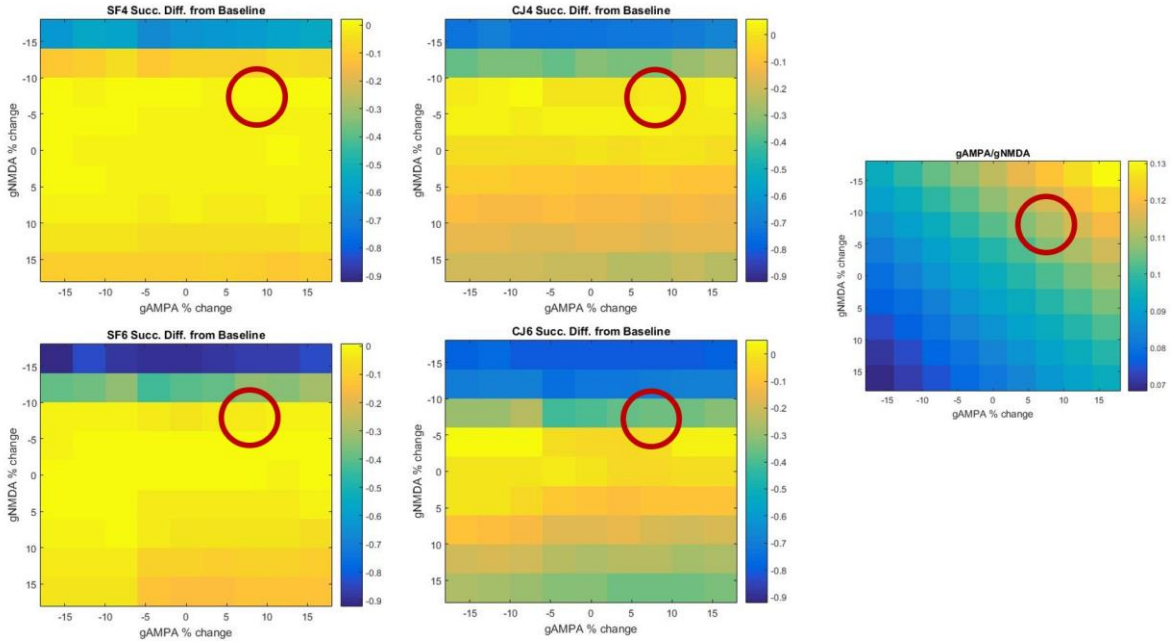

Figure 3: On the left we show the success rate differences from Baseline success rate for the single feature 4 (SF4) items, single feature 6 (SF6) items, conjunction 4 (CJ4) items and conjunction 6 (CJ6) items. The baseline values that are used for the calculations are 95% for SF4 items, 96% for SF6 items, 81% for CJ4 items and 80% for CJ6 items. The circle parameter group is the parameter group that was identified as optimum to simulate Alzheimer's visual search behaviour. On the left we show AMPA/NMDA conductance ratio changes for the parameter space used. The circle marks the set of parameters that was identified as the optimal to simulate Alzheimer's visual search behaviour.

Simulated participants' RTs and success rates across all conditions were entered into a 2 x 2 x 2 mixed-design ANOVA with the within-participants factor of condition (Single Feature/Conjunction search) and Display Size (4/6 items) and the between-participants factor of group (simulated control/simulated AD groups). This gave us the main effects and interactions presented in Table 1. A significant interaction of condition x Display Size x Group was observed for percentage success rate, but not for reaction times. For reaction time, we observed significant main effects of Display size, $F(1,28)$ =181, $p<.001$, $\eta_p^2=.866$, condition, $F(1,28)=243.4$, $p<.001$, $\eta_p^2=.897$, group $F(1,28)=276.1$, $p<.001$, $\eta_p^2=.908$ and an interaction of condition with display size, $F(1,28) = 13.9$, $p=.001$, $\eta_p^2=.332$. We did not observed significant interactions between display size and group, $F(1,28)=1.7$, $p=.191$, $\eta_p^2=.06$ or condition and group, $F(1,28)=1.4$, $p=.236$, $\eta_p^2=.05$. For success rate, we observed significant main effects of Display size, $F(1,28)=67.2$, $p<.001$, $\eta_p^2=.706$, condition, $F(1,28)=222.2$, $p<.001$, $\eta_p^2=.888$, and group, $F(1,28)=34.2$, $p<.001$, $\eta_p^2=.551$. We also observed significant interactions between condition and display size, $F(1,28)=59.2$, $p<.001$, $\eta_p^2=.682$, condition and group, $F(1,28)=26.4$, $p<.001$, $\eta_p^2=.486$ and display size and group, $F(1,28)=65$, $p<.001$, $\eta_p^2=.699$

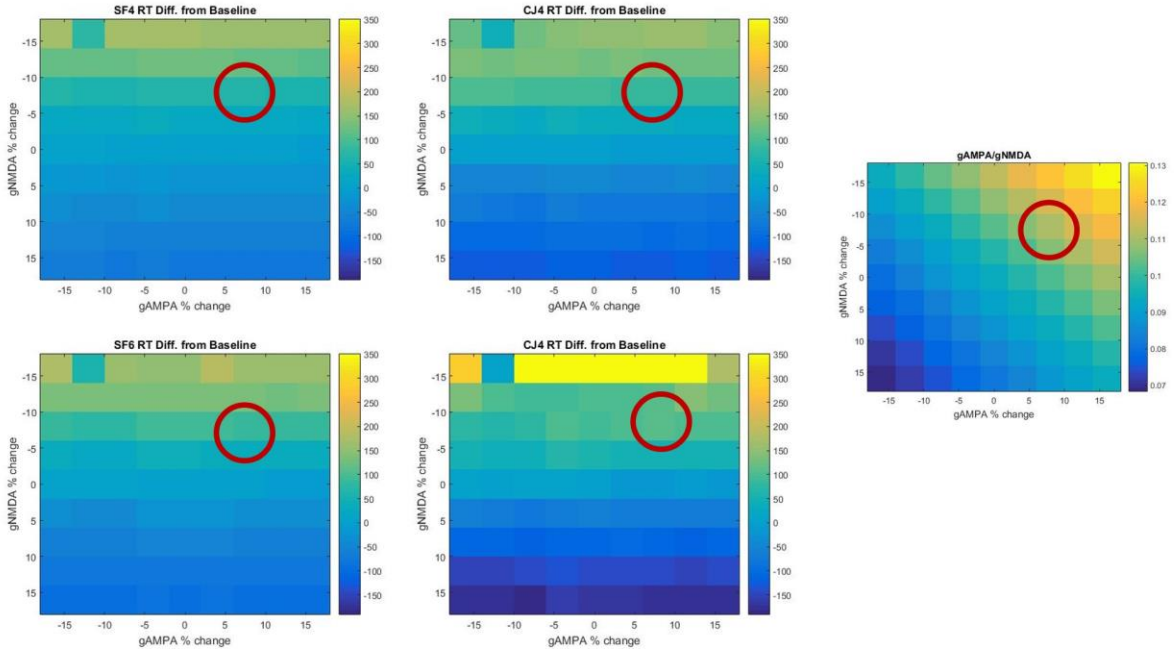

Figure 4: On the left we show reaction time difference from Baseline reaction time for the single feature 4 (SF4) items, single feature 6 (SF6) items, conjunction 4 (CJ4) items and conjunctions 6 (CJ6) items. The baseline values that are used for the calculations are 254.5 ms for SF4 items, 299.9 ms for SF6 items, 337.2 ms for CJ4 items and 432.9 ms for CJ6 items. The circle marks the parameter group that was identified as optimum to simulate Alzheimer's visual search behaviour. On the left we show again the AMPA/NMDA conductance ratio changes for the parameter space used.

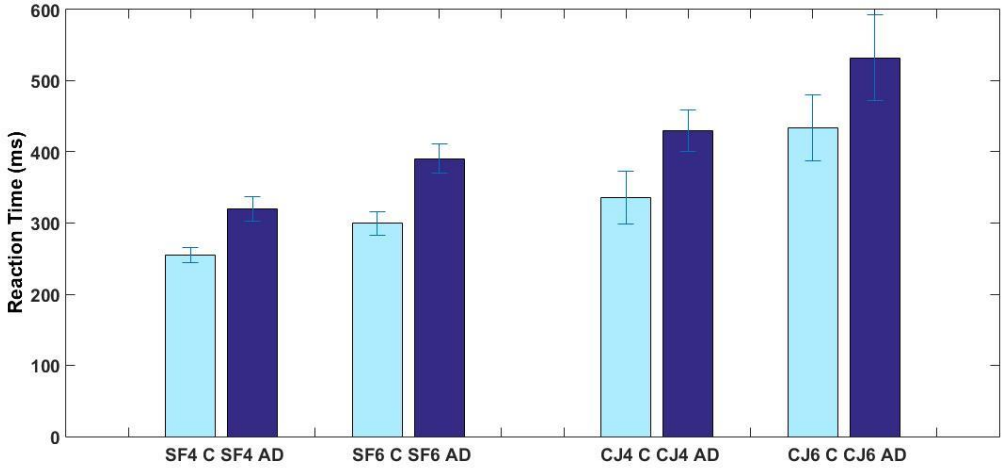

Figure 5: Bar plots for reaction rimes for simulated Alzheimer's and Baseline (simulated controls). SF4 C shows the reaction time for single feature 4 items for controls (healthy participants), SF4 AD shows the reaction time for single feature 6 items for simulated Alzheimer's patients. SF6 C shows the reaction time for single feature 6 items for controls, SF6 AD shows the reaction time for single feature 6 items for simulated Alzheimer's patients. The same applies for conjunction, where CJ4 is conjunction for 4 items and CJ6 is conjunction for 6 items.

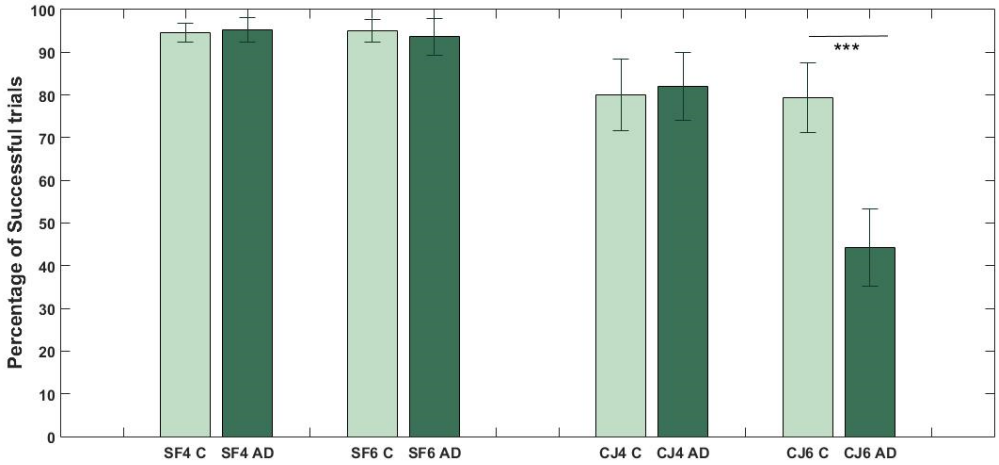

Figure 6: Bar plots for success rate for simulated Alzheimer's and Baseline (simulated controls). SF4 C shows the success rate for single feature 4 items for controls (healthy participants), SF4 AD shows the success rate for single feature 6 items for simulated Alzheimer's patients. SF6 C shows the success rate for single feature 6 items for controls, SF6 AD shows the success rate for single feature 6 items for simulated Alzheimer's patients. The same applies for conjunction where, CJ4 is conjunction for 4 items and CJ6 is conjunction for 6 items.

Table 1

ANOVAs of Percentage Success and Reaction Times, Reporting the Main Effects of, and Interactions Between, Condition (Single Feature/Conjunction Search), Display Size (4/6 Items), and Group (Baseline/AD Group)

Measure	ANOVA term	F (*df*)	*p*	η_p^2
Reaction Time	Display Size	181 (1,28)	<.001	.866
	Condition	243.4 (1,28)	<.001	.897
	Group	276.1 (1,28)	<.001	.908
	Condition x Display Size	13.9 (1,28)	.001	.332
	Condition x Group	1.4 (1,28)	.236	.05
	Display Size x Group	1.7 (1,28)	.191	.06
	Condition x Display Size x Group	.8 (1,28)	.36	.03
% Success	Display Size	67.2	<.001	.706
	Condition	222.2	<.001	.888
	Group	34.2	<.001	.551
	Condition x Display Size	59.9	<.001	.682
	Condition x Group	26.4	<.001	.486
	Display Size x Group	65	<.001	.699
	Condition x Display Size x Group	53.6	<.001	.657

Discussion

This study fits broadly into the category of Computational Psychiatry (Montague, Dolan, Friston, & Dayan, 2012; Yu & Dayan, 2002). Although majority of Computational Psychiatry approaches aim to decompose behavioural into its constituents before explaining it neural underpinnings, such as mapping decision-making into values and prediction errors, our approach aimed at providing an architectural framework under which neurobiological dysfunctions can directly explain symptomology

in Alzheimer's. The results from this work clearly demonstrate that computational modelling that bridges low level characteristics with whole system behaviour can be used to simulate attentional processes, as has also been previously shown (Eirini Mavritsaki et al., 2011; Riddoch et al., 2010), and to make that bridge in simulating Alzheimer's disease changes in attentional processing. There were significant changes observed between simulated controls and simulated Alzheimer's disease patients for success rates and reaction times, as has been previously shown (Cormack et al., 2004; Foster et al., 1999; Hao et al., 2005; Porter, Leonards, et al., 2010; A. Tales et al., 2002b; Andrea Tales & Porter, 2008) and significant interactions for condition, display size and group. This clearly demonstrates that the model was able to capture some of the changes in Alzheimer's disease attentional processing by changing the gNMDA and gAMPA parameters, simulating reduction in acetylcholine observed in Alzheimer's disease.

Although the results showed significant overall interactions for success rates, the overall interaction for reaction time was not significant. This can be attributed to the fact that the healthy simulated behaviour is at ceiling level therefore any changes due to the acetylcholine reduction might not be easily detected. Another reason might be that although acetylcholine reduction is important in Alzheimer's disease that other processes are also taking place, like changes in binding, grouping or inhibitory processes (Hao et al., 2005; Levinoff et al., 2004; Parasuraman et al., 2000). Changes in these processes are not taken into consideration in the present work, as this work aimed simply to investigate if acetylcholine changes could be simulated using the chosen approach. Although these processes were not investigated in the current work, the model incorporates all the above processes (Eirini Mavritsaki et al., 2011; Eirini Mavritsaki & Humphreys, 2016) and therefore can allow us to further investigate them in the following steps of our work. Furthermore, additional work is required to investigate where acetylcholine changes can be related to the oscillatory behaviour in Alzheimer's disease demonstrated by Mazaheri et al. (2018) thereby helping to shed light on further understanding of disease progression. The presented work therefore demonstrated that the proposed and similar modelling approaches can be used to simulate Alzheimer's disease. The following steps are to use the model to combine the changes in attentional processes which are found in Alzheimer's disease in one model and use the model to shed light on this condition. Furthermore, if this is combined with oscillatory behaviour study (Mazaheri et al., 2018) by using previously develop approaches for extracting MEG activity from similar models (Barbieri, Mazzoni, Logothetis, Panzeri, & Brunel, 2014), it may be able to provide the first step for delivering personalized treatment in Alzheimer's disease.

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