Quotations from fraudulent researcher Lynette Looi Ling's doctoral thesis published by Aston University, 2022, emphases added, citations mostly removed:

Examining Resting-State Functional and Structural Connectivity of the Attention Networks after Early Brain Insults

…Through a series of planned experiments to explore functional…and structural…connectivity in focal…and generalised…early brain insults, this thesis offers a unique lens to examine the potential use of advanced brain imaging techniques to examine brain networks that are crucial for attention functioning… In children with early life brain insults, however, the present thesis found no evidence of functional alterations between the two networks. Specifically, experimental study 1 (Chapter 3) did not reveal any significant differences in the functional connectivity between the DMN and CEN, nor between regions within the CEN in epilepsy patients when compared to typically developing children. Similarly, experimental study 3 (Chapter 5) has also failed to support the hypothesised neural network alterations in children with a brain injury as compared to healthy subjects. Moreover, the structural studies (Chapters 4 and 5) failed to provide evidence of SCN alterations between patients with a brain insult and healthy children. The lack of confirmation can potentially be explained by different factors like small sample size, and heterogeneous patient sample... pg 162

…The studies included in this thesis have shed light on the neural changes following a paediatric brain insult, especially in the DMN, which is important in sustained attention function. However, the main take-home message of this research is that further exploration into the questions posed in this research is still necessary…pg 171

…In conclusion, this thesis has investigated the potential of novel neuroimaging network analysis methods that could be used in place of behavioural measures to identify children with a brain injury who would go on to have attention problems…pg 173

…I am thankful for all the participants and their families who have contributed their effort and time to the studies whose data was used in the current thesis…pg 4

…The present study reported on data that were previously collected from a larger longitudinal prospective study that investigated social cognitive outcomes of paediatric TBI at baseline, 6- and 12-months following injury…pg 62

…The Royal Children's Hospital Human Research Ethics Committee and the Victorian Department of Education Research Ethics Committee approved the TBI study. Data in the current study were later obtained under a Material Transfer Agreement between the Murdoch Children's Research Institute and Aston University. Aston University granted a favourable ethical opinion for the secondary analysis of neuroimaging data from the TBI dataset (reference number #1083)….pg 64

…Ethical approval was obtained separately for both the healthy children and patient group. Ethical approval was obtained from Aston University Ethics Committee (reference number #888) for the controls, and ethical approval for patients was sought from West Midlands- Black Country NHS Research Ethics Committee (IRAS reference 206601)….pg 93

……Parents' written informed consent for their child's participation in the study were obtained. Verbal assent was sought from children below the age of 16, while consent was also obtained from children over 16 years and deemed capable of giving consent…pg 93

…Ethical approval was obtained separately for both the healthy children and patient group. As per previous chapter, ethical approval was obtained from Aston University Ethics Committee for the former, and ethical approval for patients was sought from NHS Research Ethics Committee….pg 118

…Healthy children were recruited either from the Birmingham community by contacting families who have previously indicated their interest in research being carried out at the Aston Brain Centre, Aston University, or are controls for a different neuroimaging study described in Chapter 5…pg 116

…Typical developing children were either recruited via Birmingham Children's Hospital outpatient clinics (children referred for non-neurological reasons like musculo-skeletal imaging or head/neck MRI where central nervous system involvement was not suspected) or through leaflets and posters placed throughout the community (i.e., schools, libraries, community group centres, and doctor's offices). Paediatric patients were recruited via Birmingham Children's Hospital when they were referred for routine MRI scans. These children were referred to radiology because of a suspected or known cerebral abnormality or brain lesion (i.e., CT evidence of a lesion, epilepsy, neurooncology, TBI, or stroke). Therefore, the imaging scans (namely fMRI) for this study were added to the patients' clinical scans…only 5 typical developing children (9–12 years, M = 10.20, SD = 1.10, 2 males, 3 females) and 13 patients (7–14 years, M = 10.31, SD = 2.18, 4 males, 9 females) were included in final analyses…pg 142

…Ethical approval was sought and obtained through an NHS Research Ethics Committee (Yorkshire and The Humber), and R&D management approval was also obtained from Birmingham Women's and Children's NHS Foundation Trust from where the participants in this study were recruited (REC

reference 17/YH/0299). Aston University also acted as a sponsor for the study (IRAS reference 222771)…pg 159

…Families were first contacted to confirm their willingness to participate in the study before study details were mailed to them. The study then obtained parents' written, informed consent for children to participate in the study, as well as for retrospective extraction of clinical data from the child's medical records at the time of recruitment. Verbal assent was also sought from children who were older than 8 years. To prepare the participants for scanning, a mock scanning session was carried out with each participant to aid in familiarising them with the scanner environment. During the scan, radiographers consistently checked on the participants and informed them if they were moving, and sequences were repeated if possible when excessive motion was detected on the image reconstruction…pg 64

…Sustained attention was assessed using Walk/Don't Walk and Sky Search Dual Task from The Test of Everyday Attention for Children (TEA-Ch), a standardised and reliable tool to access the components of attention…Due to the differences in cortical thickness, cortical surface area and cortical folding between the brains of children and adults, there is the risk of potential confounds when using a standardised adult template…

…The patient (M = 12.88, SD = 1.46) and control groups (M = 12.77, SD = 2.16) showed no significant difference in age…Patients (five males, one female) and controls (three males, five females) showed no significant difference in genders…pg 68

…Using independent t-test, no significant difference was found between the paediatric TBI patients and typically developing children…pg 71

…Indeed, there was no significant difference in functional activity in the DMN between the groups. The current findings contradict previous studies, also using similar ICA methods, which reported activity alterations in the DMN regions (i.e., increased activity in the frontal regions, reduced activity in the PCC and parietal regions) in adults after a TBI…pg 76

…In summary, the present study has shown alterations in the functional connectivity involving the regions of the DMN (PCC and mPFC) in TBI children when compared to typically developing children…pg 82

…The current study aimed to use resting-state fMRI to examine 1) functional activity changes in the DMN and CEN between patient and control cohorts, 2) functional connectivity changes between specific brain regions the DMN and the CEN between patient and control cohorts, and 3) functional connectivity changes between the regions of the DMN and CEN between patient and control cohorts…Healthy children were recruited either from the Birmingham community by contacting families who have previously indicated their interest in research being carried out at the Aston Brain Centre, Aston University, or are controls for another study. Paediatric patients with epilepsy were recruited via Birmingham Children's Hospital, where they were referred to the Aston Brain Centre for pre-surgical evaluation as part of the Children's Epilepsy Surgery Service program. In total, 24 healthy children and 26 patients with drug-resistant epilepsy (four right-hemisphere) were recruited. The four right-hemisphere patients were removed, leaving 22 patients with left- hemispheric epilepsy…pg 90

…Using Fisher's exact test, the sex distribution of the patient group (six males, eight females) was not significantly different from the control group (four males, nine females) ($p = .70$). However, the two groups were not age-matched ($t(25) = 4.13$, $p < .0001$). The data showed that the controls in the current study ($M = 11.31$, $SD = 2.72$) were significantly younger than patients with epilepsy ($M = 14.64$, $SD = 1.28$). To eliminate potential confounding influences of age on the current findings, age was used as a covariate in the analyses…pg 96

…In summary, the reduction in the left parietal found in the current study may represent neurobiological characteristics common to different epilepsies; this reduction could also be associated with cognitive deficits in patients with epilepsy…pg 107

…Using resting-state fMRI, the current study demonstrated reduced functional activity in the left parietal lobe in children with refractory epilepsy relative to healthy children. Neural alterations in children with epilepsy may result from various reasons like medication and frequency of seizures, which future studies should include into their analyses…pg 108

…In healthy adults and children, studies have found a relationship between resting-state functional connectivity and structural magnetic resonance imaging (MRI) derived measures, like the grey matter volume and cortical thickness…pg 110

…The overall aim was to investigate structural connectivity changes in children with left focal epilepsy as compared to typically developing children. Despite potential differences in structural changes between different forms of epilepsy (i.e., temporal lobe and frontal lobe), attention impairments are well established in both epilepsy types, and comparable impairments have been suggested between both groups…pg 115

…Using structural covariance networks, the current study found no significant differences between patients with epilepsy and healthy children... The absence of clinical information (i.e., medication/seizure frequencies), the influence of lesions in patients and the heterogeneous patient group however could have influenced the current study's findings. Future studies should aim to recruit a larger sample size, allowing sub-analysis of the different epilepsy subtypes, whilst controlling for medication and seizure frequency…pg 135

…Strong associations exist between brain functional and structural changes following brain insults in childhood, as evidenced by structural magnetic resonance imaging (MRI) and functional MRI (fMRI) in patient populations…pg 136

…Given the time and cost efficiency of structural MRI over fMRI, it is important to determine whether SCN changes can explain fMRI changes following a paediatric brain insult. Moreover, the current literature has shown that regardless of the nature of the brain injury, patients reported similar deficits in sustained attention, which might reflect shared brain functional and structural changes in these patients. Thus, the current study will look at patients with a range of brain injuries, inclusive of epilepsy, stroke, brain tumour and TBI…pg 141

…Nonetheless, the lack of differences does suggest that the functional and structural characteristics of children with a brain insult may not differ significantly from typically developing children. However, the current findings are in contrast with existing functional and structural studies that have shown neural disparities between children with a brain insult and controls. Thus, several reasons that could explain the disparities between the current findings and other studies have been discussed, including the heterogeneous nature of the pathological basis of the lesions, the severity of injury, the time since the injury, and potential differences in cognitive level of the patients…pg 159

…The current study found no significant differences in both the resting-state fMRI and SCN between patients with a brain insult and typically developing controls…Instead, the current study highlights the importance of recruiting a larger sample size to also carry out sub-analyses…This is important because attention impairments have been associated with learning problems and poor academic achievement. Therefore, being able to separate children with a poor outcome (like attention problems) from those with a good outcome will allow for early treatment and a higher chance of recovery….pg 160

…Attention impairments in children are common after brain injury, and there is enormous potential for quantitative neuroimaging techniques, specifically functional and structural magnetic resonance imaging (MRI), to improve early identification of affected children by examining relevant neural networks. The current thesis represents an important step towards examining the use of these

methods in paediatric cohorts. Attention is important to our daily life, as it allows us to ignore irrelevant distractors and focus on relevant information. It plays a vital role in both explicit and implicit learning, and consequently in academic achievement (Posner & Rothbart, 2014; Rabine & Coie, 2000). Importantly, attention is not a single process but instead one made up of several types of cognitive processes, which are supported by their own distinct sets of brain regions (Luo & Maunsell, 2019; Raz, 2004). There is ample evidence, particularly in the adult brain injury population, that functional and structural alterations to these brain regions are associated with attention impairments (Bonnelle et al., 2011; Sharp et al., 2011). Less is known about the effects of brain injury on the regions associated with attention problems in children with brain injuries, despite this population's susceptibility to attentional impairments (Bloom et al., 2001; Konigs et al., 2015). Furthermore, the continuous development of connections between regions in the brain across childhood potentially increases the susceptibility of children's brains to insults; this may depend in part on whether the injury is focal or generalised in nature (Harris, de Rooij, & Kuhl, 2019). Cortical networks are therefore important to our understanding of the attentional consequences of early-life brain changes. Advances in neuroimaging techniques such as functional MRI (fMRI) allow us to examine injury- or disease-related changes in the brain and can reveal relationships between specific cognitive impairments and the neural substrate underpinning them (Scheibel, 2017; Yin, Li, Zhao, & Feng, 2013). Advances in quantitative brain imaging techniques allow us to move beyond simple lesion-based approaches and instead examine the complex neural networks underlying attention in diseased and healthy development. Identifying these networks could help us identify children at risk of poor attentional outcomes…

…The current chapter provides an overview of acquired brain injury (ABI) and its consequences. It then discusses the disparity between the brains of children and adults, and the impacts this disparity has on their respective responses to brain injury…pg 14

…ABI is an umbrella term that includes any neurological damage sustained after birth that is not congenital or degenerative. There are two subtypes of acquired brain injury. The first subtype, known as traumatic brain injury (TBI), is caused either by external open or closed trauma to the head; closed-head injuries refer to injuries that do not penetrate the brain. The second type of acquired brain injury results from a medical condition or disease processes within the body, and does not involved any external mechanism (for example, stroke – Barker, Gibson & Robinson, 2018). According to Kraus, Fife, Cox, Ramstein, and Conroy (1986), common causes of TBI include falls, recreational activities and motor accidents; common causes of non-traumatic brain injury include brain tumours, encephalitis, stroke and neurological disorders... ABI does not refer to a single negative developmental process, but rather a situation in which a person, previously intact from a neurological perspective, subsequently

acquired some form of brain pathology that may lead to the physical, neurocognitive and psychological impairments to be discussed below…pg 15

…The developing brain in children is typically assumed to have greater plasticity than the adult brain because of the processes underpinning plasticity, which include neurogenesis (formation of new neurons), apoptosis (programmed cell death) and activity-dependent synaptic plasticity (changes in neuronal connectivity as a result of synaptic transmission)…pg 20

…The vulnerability of the cortical (including frontal, prefrontal and parietal) and subcortical brain structures (including the limbic system, thalamus, hypothalamus, reticular formation, and basal ganglia) that support general attention processes to brain injury could potentially explain the prevalence of attention deficits…pg 23

…Attention is, however, recognised to be not be a single process but rather a complex process consisting of a group of attention sub-processes or components… Therefore, to better understand the impact of brain injury on attention, it is important to understand the components of attention, which will be further discussed in the following section via prominent attention models pg 24

…1.8Aims of Thesis

…Sustained attention plays a vital role in cognitive functions and ultimately functional outcomes, including academic performance. Across different types of brain insults, including TBI and non-traumatic brain injuries such as epilepsy and stroke, sustained attention deficit is the most commonly reported problem following brain injury in children. The vulnerability of sustained attention to brain injury is because the neuronal substrates supporting attention, such as the frontal and parietal brain regions, are commonly damaged by brain insult. Given that sustained attention impairments are found across brain insults, it is likely that there are overlapping neural alterations in these patients that underlie the impairments. Current literature has, however, highlighted the presence of disorder-specific neural changes in the networks associated with sustained attention. It is therefore important to explore different injury types, characterised by different lesions or pathologies, in order to obtain a better understanding of attention and its underlying networks….In the following chapters, studies examining alterations in the functional and/or structural connectivity in the brain regions underlying sustained attention in patients with a brain insult are presented. Chapter 2 presents results from a pilot study that examined resting-state fMRI functional changes between regions within the DMN in children with TBI compared to typically developing children. Based on the current literature, the study expected to find reduction in the functional connectivity within the DMN in paediatric patients. Given this thesis's interest in early brain insults, Chapter 3 further explores resting-state fMRI changes in the

DMN and CEN in children with epilepsy as compared to typically developing children. Based on the present studies, Chapter 3 hypothesises reduced functional connectivity between regions within the DMN and within the CEN, and between the DMN and CEN regions in paediatric patients. Given the relationship between functional and structural connectivity, Chapter 4 examines structural covariance network alterations across the whole-brain, and specifically between regions within the DMN and within the CEN, and between the DMN and CEN regions, in children with epilepsy as compared to healthy children. Based on recent studies, the study expected to find alterations in the SCN in paediatric patients. Finally, Chapter 5 examines changes in both SCN and resting-state fMRI across the whole-brain, and specifically between regions within the DMN and within the CEN, and between the DMN and CEN regions, in paediatric patients with a brain insult compared to typically developing children. The chapter hypothesise 1) functional and structural alterations in paediatric patients, and 2) similarities across the brain regions that demonstrate functional and structural alterations. The final chapter in the thesis, Chapter 6, discusses the overall findings of the experimental chapters, the implications of these findings, and the limitations and directions for future studies…g 56

…I am also thankful to Kelvin Ho – Kor, thank you for being so patient with my pessimism during my write-up year, and for the constant reminders that a life outside my PhD exists…pg 4