Sleep, Memory, and the Alcohol-Exposed Brain: Investigating the relationship between SWS Features, Childhood Hippocampal Volume and Declarative Memory in Young Adults with Fetal Alcohol Spectrum Disorders

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TBRJUL002

A Dissertation submitted in fulfilment of the requirements for the award of the degree of Master of Arts (Psychological Research Specialisation)

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2025

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Acknowledgements

Before starting this journey, I was unaware of the challenges that come with starting a master's degree let alone writing a dissertation. However, I did not surpass these obstacles nor celebrate my successes alone and for that I wish to thank several people for their continued support, guidance and contributions to this work.

Firstly, I would like to express my gratitude to my supervisor, Associate Professor Gosia Lipinska for her mentorship and belief in my work. Without her incredible depth of knowledge on all things sleep and memory, as well as research expertise and enthusiasm for sleep research, this thesis would not have been possible. I am thankful for the opportunity I was afforded to develop academically and professionally within the research space while working alongside her to produce a piece of writing I am so proud of. Thank you for all the meticulous edits, meetings and encouragement.

I also extend my gratitude to my co-supervisor, Dean of Humanities Kevin Thomas for his guidance and support during the data collection process. Thank you for your continued belief in my academic capabilities and guidance through the many challenges that come with the research process.

My sincere thanks also go to the Wayne State University Team, Joseph Jacobson, Sandra Jacobson and Neil Dodge for choosing me to be a part of such an incredible study and research team. The knowledge I have gained is invaluable and your continued passion for the field has been inspiring. Thank you for the wisdom you have shared and supervision regarding my work.

I also wish to thank Dan Denis for his expertise and advice on the minute details relating to sleep data as well as the framework provided for its statistical processing.

A heartfelt thanks is also extended to the FASD research assistant team, Rhiannon Chernotsky, Annette du Plessis and Joel Mvula for making the sleep laboratory experience so memorable and the many mountainous obstacles we faced seem as small as mole hills.

I also give a special thanks to Thumira Pillay who kept me grounded during our long nights in the sleep laboratory and the many challenges that came with untangling the data. Her continued support both emotionally and academically has been immeasurable. I am so grateful for our friendship and that we were able to share this journey and its obstacles, but more importantly its successes, together.

To my family and friends thank you for the encouragement through the long sleepless nights, helping to edit my work and being there throughout this process always pushing me to do more.

Lastly, thank you to all the participants who partook in our research, this research would not have been possible without you.

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List of Abbreviations

AA	Absolute Alcohol
AA/dd	Average Ounces of Absolute Alcohol per Drinking Day during Pregnancy
AASM	American Academy of Sleep Medicine
ACSENT	Applied Cognitive Science and Experimental Neuropsychology Team
ADHD	Attention Deficit Hyperactivity Disorder
AI	Arousal Index
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ARBD	Alcohol Related Birth Defects
ARND	Alcohol Related Neurodevelopmental Disorder
ASD	Autism Spectrum Disorder
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory Second Edition
CMS	Children’s Memory Scale
CP	Coupling
CSHQ	Children's Sleep Habits Questionnaire
CVLT	California Verbal Learning Test
CVLT-C	California Verbal Learning Test for Children
DD	Drinking Days
DOA	Drugs of Abuse
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECG	Electrocardiography
EDF	European Data Format
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
FFT	Fast Fourier Transform

HC	Healthy Controls
HE	Heavily Exposed
HIC	High Income Country
HV	Hippocampal Volume
ICV	Intracranial Volume
LMIC	Low- and Middle-Income Country
LOS	Lightening of Sleep
MRI	Magnetic Resonance Imaging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NREM	Non-Rapid Eye Movement
PAE	Prenatal Alcohol Exposure
PFAS	Partial Fetal Alcohol Syndrome
PSD	Power Spectral Density
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid-eye Movement
SE	Sleep Efficiency
SES	Socio-Economic Status
SO	Slow Oscillation
SOL	Sleep Onset Latency
SQ	Sleep Quality
SSS	Stanford Sleepiness Scale
SWA	Slow-wave Activity
SWS	Slow-wave Sleep
THC	Tetrahydrocannabinol
TIB	Time in Bed
TLFB	Timeline Follow-back Interview
TRN	Thalamic Reticular Nucleus
TST	Total Sleep Time
UCT	University of Cape Town
WASO	Wake After Sleep Onset

WRAML-II	Wide Range Assessment of Memory and Learning, Second Edition
WSU	Wayne State University

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Abstract

Prenatal alcohol exposure (PAE) has detrimental effects on sleep and memory. Children with PAE have shown a) clear disruptions to sleep maintenance with some evidence pointing to altered slow-wave sleep (SWS) and b) deficits in short-term verbal memory recall, persisting into young adulthood, with some evidence of consolidation difficulties over this timescale. Furthermore, the hippocampus, a brain region crucial for memory encoding and facilitating sleep-dependent consolidation, is also negatively impacted by PAE. However, the connection between these abnormalities has not been explored despite the well-documented relationship between SWS, the hippocampus and memory consolidation. Given these known associations I aimed to investigate systematically, in a young adult population, 1) whether PAE was associated with differences in SWS architecture, childhood hippocampal volume and memory retention (a behavioural measure of consolidation) and 2) whether individuals with PAE (compared to those without exposure) with smaller hippocampi and altered SWS had poorer memory retention. **Methods:** Data from 76 young adults (21.68 years), from the Cape Town Longitudinal Cohort, were used from night two of a three-night sleep study. Participants were grouped as having fetal alcohol syndrome (FAS)/partial FAS; $n = 24$), non-dysmorphic heavily exposed (HE; $n = 23$) and healthy controls ($n = 29$). Participants completed evening and morning WRAML-II story and word-list tasks, separated by an 8-hour polysomnographically-recorded sleep interval. Maternal reports of PAE and hippocampal data were collected in earlier studies. **Results:** Individuals with a diagnosis of FAS/PFAS had more SWS arousals than controls ($p = .018$) and smaller left ($p = .029$; $p = .008$) and right hippocampi ($p = .007$; $p = .006$) than both HE and control individuals, respectively. Additionally, those with FAS/PFAS had poorer retention for the story task than controls ($p = .021$) with HE individuals trending towards the same pattern ($p = .055$). Results for

dose-related exposure mimicked these results with higher exposure associated with poorer story retention ($p < .001$). Modelling revealed that dose-related PAE and fast spindle duration, coupling percentage and strength were important for predicting story-related information. Particularly, retaining contextual information relied on shorter fast spindles that coupled more frequently and less consistently. Greater coupling strength was only detrimental to story consolidation for individuals with smaller left hippocampi. Lastly, word-list retention was more strongly predicted by FASD status and SWS macro-architecture whereby only word-list retention for controls benefitted from more SWS. **Conclusion:** The findings link PAE to poorer sleep-dependent memory consolidation and suggest that PAE may disrupt the SWS-declarative memory relationship. For example, the typical benefit of greater coupling strength seems to have a paradoxical effect in those with smaller hippocampi, who are more likely to have PAE, suggesting a disruption in the mechanism of consolidation. The findings also provide novel insights into which aspects of SWS benefit the retention of contextual and discrete verbal declarative tasks. In the future interventions that target sleep can be developed to ameliorate memory deficits in this population and more specifically target micro-architecture for the learning of contextual information and macro-architecture for learning of discrete information.

Key Words: Slow-wave sleep (SWS); Fetal alcohol spectrum disorders (FASD); prenatal alcohol exposure (PAE); memory consolidation; hippocampus

Introduction

Fetal Alcohol Spectrum Disorders (FASD) are a prevalent yet preventable group of neurodevelopmental disorders, associated with prenatal alcohol exposure (PAE). Although global health initiatives have strived to spread awareness of the dangers of consuming alcohol during pregnancy, global prevalence rates remain around .77%. These rates differ widely across regions with Europe and North America being between 2-5% while the Eastern Mediterranean region sits at 0.1% (Lange et al., 2017; Wozniak et al., 2019). However, South Africa remains the country with the highest rate of FASD cases globally at 11.1% above Croatia and Ireland, largely due to entrenched drinking patterns stemming from the Apartheid 'dop' system (Jacobson et al., 2008; Lange et al., 2017). Although high-income countries (HICs) may have the means to withstand the subsequent social and economic burdens that arise from FASDs and comorbid conditions, there is significant burden associated with the condition for low- and middle-income countries (LMICs), such as South Africa, to bear (Centers for Disease Control and Prevention, 2024). Thus, FASDs should continue to be a priority in research and awareness campaigns, especially in LMICs.

FASDs are classified into four subcategories that largely indicate the severity of the disorder and are associated with both timing and amount of PAE namely, the more severe fetal alcohol syndrome (FAS) and partial fetal alcohol syndrome (PFAS), and less severe alcohol-related neurodevelopmental disorder (ARND) and alcohol related-birth defects (ARBD; (Popova et al., 2021). As a syndrome, FASDs are characterised by a range of symptoms that encompass marked physical, neuropsychological and behavioural difficulties that occur to varying degrees (Popova et al., 2021). These symptoms arise from the effect of the teratogen ethanol on the cellular and genetic makeup of the fetus at different developmental stages (Popova et al., 2021).

Research into FASD has generally focussed on assessing biomarkers, outlining diagnostic criteria and neuroimaging with some research exploring behavioural and cognitive abnormalities (e.g. Chabenne et al., 2014; Cook et al., 2016; Lebel et al., 2011; Kingdon et al., 2016).

Behaviourally, children with FASD have shown marked subjective sleep difficulties, typically derived from parental self-report, compared to unexposed children, which may be both at the root of their cognitive difficulties as well as exacerbate them (e.g. Ipsiroglu et al., 2019). Only a handful of studies have examined sleep objectively in this population through actigraphy or polysomnography (PSG; M. L. Chen et al., 2012). Thus, research into which areas of sleep are disrupted in these individuals has been largely neglected despite its importance related to cognition. However, some findings suggest disruptions to slow-wave sleep (SWS) macro- (Apuzzo et al., 2020) and micro-architecture (Inkelis & Thomas, 2018), which can only be measured using PSG.

In the field of cognitive research for children with FASDs, executive dysfunction has been a prioritised research focus, especially the domain of working memory (see Kingdon et al., 2016 for a review). However, altered brain development in individuals with FASDs has also been associated with other cognitive abnormalities outside of the executive domain, including declarative memory deficits (du Plooy et al., 2016). These memory difficulties coincide with the known alterations that occur within the hippocampus due to PAE (Lebel et al., 2011).

In another area of research, it is well established that SWS and declarative memory are intrinsically linked as the consolidation of declarative memory traces occurs during this sleep period with a central role played by the hippocampus (Gais & Born, 2004; Schönauer, 2018). This is through the generation of synchronised sleep features known as hippocampal ripples, spindles and slow-oscillations (SOs) which are markers of sleep quality (Klinzing et al., 2019).

Thus, altered SWS macro- and micro-architecture experienced by those with FASD, together with hippocampal alterations, may contribute to their memory deficits.

In this thesis, I aim to investigate the associations between declarative memory performance, SWS macro- and micro-architecture and previously collected hippocampal volume data, in young adults with and without FASD in South Africa. This will be achieved through the analysis of objective PSG sleep data that includes typical measures of SWS as well as more nuanced analyses to describe SWS micro-architecture.

Literature Review

Alcohol remains one of the most consumed teratogens despite its known detrimental effects on fetal development and risks to mortality (Lange et al., 2017; Popova et al., 2021). The immediate, lifelong and toxic effects of prenatal alcohol exposure (PAE) are associated with a group of neurodevelopmental disorders known as FASDs which are particularly prevalent in the Western Cape province of South Africa (13.5-20.8%; May et al., 2013). This is largely due to the historical implementation of the Apartheid 'dop' system in which farm workers were paid in wine, leading to a legacy of alcohol abuse in certain communities. Although research is underway to establish possible prenatal treatment options that may mitigate some of the adverse effects of ethanol, FASDs and their accompanying comorbidities are currently lifelong (Jacobson et al., 2018; Popova et al., 2021).

Alcohol is known to be neurotoxic to a developing fetus through directly instigating cell death and indirectly via reduced neurogenesis and genetic and endocrine changes (Popova et al., 2021). These biological effects result in the range of symptoms that characterise FASDs which vary in severity across diagnostic categories. Physically, the disorders are associated with lower-than-normal growth rates and smaller head circumferences. FAS specifically, is associated with hallmark facial abnormalities, such as short palpebral fissures, a smooth philtrum and a narrow vermillion border (Jacobson et al., 2021). These facial features are usually less prominent or not seen in other FASDs and may diminish over time (Jacobson et al., 2021). Other maternal factors are also associated with increased risk of developing FASD after PAE, including lower maternal weight and SES, nutritional deficiencies and being a smoker (Popova et al., 2021).

Apart from the physical features, FASDs are associated with marked, lifelong cognitive and behavioural difficulties hypothesised to be due to the effects of ethanol byproducts on the

developing brain (Mattson et al., 2019; Popova et al., 2021). This has been supported by neuroimaging evidence of reduced total brain volume and reductions in specific regions such as the corpus callosum and hippocampus (Lebel et al., 2011) as well as evidence of poorer sleep (Inkelis & Thomas, 2018) and declarative memory (du Plooy et al., 2016).

A wide body of literature shows that SWS and declarative memory are intrinsically linked, as the consolidation of declarative memory traces occurs during this sleep period through hippocampal-neocortical dialogue (Klinzing et al., 2019; Schönauer, 2018). Thus, abnormal SWS coupled with deficient hippocampal development in individuals with FASDs may contribute to their memory deficits. Still, these disturbances have not been adequately studied in tandem in this population, despite their neurobiological connection.

Slow Wave Sleep

Sleep is an important biological state that is commonly divided into two broad categories, measured using electroencephalography (EEG): non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Alger et al., 2014). NREM sleep is further separated into stages N1, N2 and SWS, each with their own unique characteristics and functions. Of these stages, SWS is the deepest sleep stage and usually accounts for 10-25% of time spent asleep which describes its macro-architecture (Pei et al., 2008). SWS predominantly consists of highly synchronised, large amplitude (75μV) oscillations in the delta (1-4 Hz) and SO (0.5-1 Hz) frequency ranges that are generated by the frontal cortex (Fehér et al., 2021; Klinzing et al., 2019). These waves represent large-scale alternating neuronal bursts of high activity (depolarisation) and quiet periods of low activity (hyperpolarisation; Fehér et al., 2021; Klinzing et al., 2019).

Regarding SWS micro-architecture, spindles (11-16 Hz), which are a prominent feature of N2 sleep, also occur during SWS at a rate of 1-6 spindles per minute (Fernandez & Lüthi,

2020; Troester et al., 2023). The thalamic reticular nucleus (TRN) is integral to their production and temporal association with other SWS oscillations whereby 50-70% of spindles coincide with an SO in a process known as coupling (Fernandez & Lüthi, 2020). Coupling refers to the phenomenon of SOs and spindles co-occurring, as a result of SO depolarisation which drives spindle production through corticothalamic tracts (Fernandez & Lüthi, 2020; Mölle et al., 2011). Spindles can be further broken down into fast (12-16Hz) and slow spindles (9-12 Hz) that occur predominantly in central and frontal regions within the cortex, respectively (Fernandez & Lüthi, 2020; Mölle et al., 2011). To determine their presence during SWS periods other techniques are required to tease them apart from the dominating slow frequencies. Such techniques to analyse sleep EEG data have become more popular and refined over recent years and have allowed us to look beyond the hypnogram. These include spectral analysis and fine-grain automated spindle and SO detection (Denis et al., 2021a, 2021b). Spectral analysis is the transformation of EEG waveforms by Fourier analysis to analyse the power spectral density (PSD; derived from the amplitudes of the EEG waves) in specified frequency bands over a night of sleep or specific sleep periods (Denis et al., 2021b). Although all frequency power bands are evident across sleep, delta power or slow-wave activity (SWA) is the most dominant during SWS as a micro-architecture marker of sleep-depth (Dijk, 2009). SWA arises from neurons' need to rest which increases after wake, sleep deprivation and heavier cognitive use which consequently promote the homeostatic synaptic changes that drive the need to sleep (Dijk, 2009; Gu et al., 2023; Huber et al., 2004). SWA declines throughout the night, indicating restorative sleep as neuronal homeostasis is re-established (Dijk, 2009; Hejazi et al., 2024).

In relation to this there is some discrepancy in the literature with regards to definitions of SWS-depth. SWA and delta activity are used interchangeably to describe the amount of spectral

power around the delta frequency band in a period of sleep (Finlay & Van Dongen, 2024; Göder et al., 2006; Hejazi et al., 2024). However, others characterise SWA as an umbrella term describing delta activity and SO activity together (Fehér et al., 2021; Lanquart et al., 2018; Léger et al., 2018). The frequency ranges that are chosen for these characteristics also vary across studies. In this paper I have chosen to view SWA as the umbrella term (0.5-4Hz) with delta activity (1-4Hz) separate from SO activity (0.5-1Hz) which mimics the American Academy of Sleep Medicine's (AASM) definition of the delta range, most definitions of SWA and a more conservative SO range that includes the most common 0.8Hz SO frequency (Ngo et al., 2013).

SWS and its concomitant macro- and micro-architecture characteristics have been associated with both physical and cognitive processes, particularly declarative memory.

SWS and Memory

Memory is an essential aspect of the human experience and is underpinned by a variety of neurobiological systems, for a review please see (Squire & Dede, 2015). I will be focussing on declarative memory for neutral stimuli as it relates to sleep-dependent consolidation processes assessed through the behavioural measure known as retention. Retention describes the amount of information preserved over a period of sleep. The declarative memory system is neurobiologically governed by the hippocampal formation and neocortex (Squire & Dede, 2015). Thus, physical aspects of these structures, such as size, may be indicative of the functionality and efficiency of the structure, consequently affecting memory performance. Indeed, volumetrically the hippocampus has been shown to be associated with declarative memory performance. A meta-analysis of 25 studies on healthy children and adolescents and another study on healthy adult males revealed that larger hippocampal volumes are associated with better declarative memory recall (Botdorf et al., 2022) and retention (Pohlack et al., 2014). In further support,

Frase et al. (2020) also found that healthy adults with smaller volumes in hippocampal, parahippocampal and medial prefrontal cortex regions had poorer declarative memory retention, although this association did not depend on overnight SWS micro-architecture. Other studies have both supported and contradicted this finding when examining specific hippocampal subfields or regions. For example, adults with smaller right hippocampal heads, reduced dentate gyri and larger bodies perform better on declarative recall while children benefit from larger left hippocampal tails (Daugherty et al., 2017; de Master et al., 2014). The benefit of smaller volumes is posited to be as a result of neuronal pruning, increasing hippocampal efficiency (Daugherty et al., 2017; de Master et al., 2014; Foster et al., 1999).

In order to recall information, it must first be encoded whilst awake and then consolidated during sleep (Squire & Dede, 2015). The consolidation process is continuous and involves transferring fragile memory engrams, which are memory blueprints held tentatively between neurons, to the cortex for later retrieval (Squire & Dede, 2015).

There are two main theories for the consolidation of neutral declarative memories, namely *active systems* and *synaptic homeostasis*. For this paper I will only focus on *active systems.* This theory describes how brain regions activated during declarative memory encoding are reactivated repeatedly and in quick succession during SWS. The theory posits that memory traces are made stable through the repetitive synchronisation of sleep micro-architecture events such as hippocampal sharp-wave ripples, thalamic spindles and SOs in the neocortex (Klinzing et al., 2019; Marshall et al., 2006; Mölle et al., 2002). This synchronisation is hypothesised to both relocate engrams to the cortex and then bind together separately encoded components of a memory (e.g. visual and auditory) from their respective neocortical regions, strengthening the synapses for long-term potentiation and recall (Klinzing et al., 2019).

The *active systems model* of memory consolidation is supported by evidence that highlights the critical role SWS macro- and micro-architecture in this process. Behavioural evidence shows that the recall of declarative memory improves after periods of early SWS-rich sleep as opposed to later REM-rich sleep (Diekelmann et al., 2009; Gais & Born, 2004; Plihal & Born, 1997). Additionally, more time spent in SWS naturally or through experimental manipulation is associated with improved recall of items learnt prior to the sleep period (Barham et al., 2016; Marshall et al., 2006; Perrault et al., 2019; Takashima et al., 2006). These findings demonstrate the importance of SWS macro-architecture for the consolidation of neutral declarative memory.

Other studies have shown that SWS micro-architecture, including SWS-depth, spindles and coupling events, are active components of sleep-dependent memory consolidation. For example, artificially boosting each of these features have provided robust evidence for the SWS-consolidation relationship as the manipulated SWS-depth (e.g. SWA; Barham et al., 2016; Marshall et al., 2006, 2004; Ngo et al., 2013; Ngo & Staresina, 2022; Sánchez-Corzo et al., 2024), spindles (Leong et al., 2022; Ngo et al., 2013; Ngo & Staresina, 2022; Perrault et al., 2019) and coupling events (Ngo et al., 2013; Sánchez-Corzo et al., 2024) benefitted declarative memory consolidation. Of note, SWA has also shown to be involved in declarative consolidation as SWA specifically increased in brain regions associated with task encoding and this increase was associated with improved performance highlighting its beneficial role in memory formation (Huber et al., 2004).

With regards to spindles, two meta-analyses have investigated them as either independent oscillations (Kumral et al., 2023) or coupled oscillations (Ng et al., 2024). From the 53 studies examined by Kumral et al. (2023) the findings revealed that spindles and declarative memory

consolidation are associated. Indeed, spindles and coupling events have increased after heavy periods of declarative learning, the latter of which is indicative of the synchronised SWS oscillations that propel consolidation (Gais & Born, 2004; Gais et al., 2002; Mölle et al., 2004). Interestingly, classifying a spindle as fast or slow did not influence this relationship while spindle frequency and increased power were the strongest moderators (Kumral et al., 2023). This coincides and contradicts other studies that have both reinforced the importance of spindle power while demonstrating that this was specific to fast spindles that are more implicated in consolidation processes (Mölle et al., 2004, 2011). In addition, spindle density, duration and amplitude were also influential for consolidation though to a lesser extent (Kumral et al., 2023). Thus, from the literature there seems to be clear evidence that independent spindle parameters are important for consolidation while it is unclear whether spindle type (fast or slow) is relevant for sleep-dependent consolidation (Kumral et al., 2023; Mölle et al., 2004, 2011).

Conversely, spindle type is clearly relevant when considering coupling events. A meta-analysis of 23 studies by Ng et al. (2024) revealed that fast spindle coupling parameters tended to be more influential for declarative memory consolidation in adults, in comparison to slow spindles. This has been echoed by Mölle et al. (2011) who found that only fast spindles were tied to SO depolarisation and worked in a feedback loop to drive the subsequent amplitude and 'train' of SO waves after declarative learning, while the opposite pattern was revealed for slow spindles. Thus, learning may drive more fast spindle activity at the initialisation of an SO train which propels it to be longer and increased in power. Specifically, fast spindle coupling phase (position of coupling on the SO) and fast spindle amplitude (which is used to calculate power) had strong associations to declarative consolidation. Although they did not specify spindle type, Mikutta et al. (2019) and Weiner et al. (2024) found that spindles coupling during the up-state of the SO

were more beneficial to declarative memory consolidation compared to those whose spindles coupled after or before the up-state. Coupling strength (consistency with which coupling events occur at the same phase of the SO) was also strongly associated with consolidation, although not in relation to a particular spindle type (Ng et al., 2024). However, this relationship was weaker for Mikutta et al. (2019). Coupling percentage (number of spindles coupled to SOs) also demonstrated a positive relationship with consolidation for declarative information, although it was weaker than coupling phase and strength and was similarly unrelated to spindle type.

Therefore, although independently spindle type may not be strongly related to retention of declarative information, when examining coupling, a more robust connection between fast spindles and memory was observed that was not revealed for slow spindles. Slow spindles may reflect another mechanism of the consolidation process (Mölle et al., 2011). It may be that most studies examining coupling group spindle types together, which may muddy the results, diluting their effect for coupling strength and percentage in relation to consolidation. Nevertheless, the role of fast spindles, particularly regarding coupling processes and their influence on retention is evident.

The gathered evidence points to the important role of SWS macro- and micro-architecture for neutral declarative memory retention. Specifically, the research emphasises the crucial role of independent spindle frequency and power as well as fast spindle amplitude, coupling phase, coupling strength and coupling percentage for consolidation. Coupling measures are more reflective of consolidation processes given that they indicate inter-regional communication between brain regions during sleep that are involved in moving and strengthening memory traces. Nevertheless, poor quality SWS disrupts this process, resulting in poorer declarative memory performance.

Poor SWS Quality and Memory. Poor quality sleep has major consequences for one's cognitive and general health (Halstead et al., 2021; Mukherjee et al., 2015). Importantly, the consolidation of declarative memory is highly sensitive to sleep quality. Many studies have demonstrated that the recall of neutral declarative material was superior after periods of sleep compared to periods of wakefulness in healthy individuals, and that disrupted sleep was detrimental to memory recall (Ellenbogen et al., 2006; Gais et al., 2006; Lipinska & Thomas, 2019; Payne et al., 2012). These studies demonstrate that sleep in general strengthens neutral declarative memory traces compared to no or disrupted sleep which negate this process by preventing or disrupting consolidation. Animal studies have also shown that NREM fragmentation is associated with impaired hippocampal-dependent memory consolidation (M. L. Lee et al., 2016; Tartar et al., 2006; C. P. Ward et al., 2009). In humans, specific deprivations to SWS were associated with poorer verbal memory consolidation, although this effect was not only specific to SWS: the same was found for the REM-deprived condition. This suggests that both stages, and in fact the continuity of a night's sleep is likely to be supportive of memory consolidation (Casey et al., 2016). The effects of poor sleep quality on measures of declarative memory are also evident when assessing conditions in humans that result in altered or fragmented sleep architecture such as insomnia and obstructive sleep apnea. Insomnia, which involves reduced sleep time and more fragmented sleep has been associated with less SWS than healthy participants and with poorer declarative memory consolidation or alterations compared to controls (Backhaus et al., 2006). Patients with obstructive sleep apnea also tend to experience more fragmented sleep, resulting from awakenings due to breathing pattern changes (Gu et al., 2023). Rising with disease severity, those with sleep apnea tend to experience more fragmented sleep, less SWS and lower SWA, spindle density and frequency (Gu et al., 2023). They are also

known to experience declarative memory difficulties (Daurat et al., 2008). Djonlagic et al. (2021) showed that treatment of patients' conditions bettered their SWS and SWA and that these enhancements were associated with their improvements in the declarative memory task from baseline. In summary, poor-quality sleep is strongly related to impairments in memory processes. This is important to consider in relation to those with FASD who suffer from both disrupted sleep and memory deficits.

FASD and Sleep

Subjective sleep difficulties arising in children and adolescents with FASDs is supported by considerable evidence. A qualitative analysis of narratives and diary entries by parents have reported increased movement and restlessness during sleep as well as trouble falling and staying asleep (Ipsiroglu et al., 2019). Furthermore, the article by Jan et al. (2010) indicates the increased awareness of these sleep perturbations in multi-disciplinary teams of medical professionals with suggestions for interventions targeting better sleep hygiene. Use of the Children's Sleep Habits Questionnaire (CSHQ) by parents has also highlighted that children with FASDs appear to experience generally poor sleep quality evidenced through increased sleep latency, parasomnias, more nighttime awakenings, shorter sleep duration and increased likelihood of sleep disorders in comparison to healthy controls (Chandler-Mather et al., 2021; M. L. Chen et al., 2012; Dyląg et al., 2021; Ipsiroglu et al., 2019; Wengel et al., 2011).

Despite limited research assessing the objective sleep patterns of children with FASDs they have largely supported the subjective accounts. To characterise the sleep architecture of children and adolescents with FASD, objective measures such as actigraphy and PSG have been used. Of the gross sleep architecture disruptions that have been reported, many seem to coincide with the subjective sleep data. The most consistently reported outcome is that of individuals with

FASDs having high indices of sleep fragmentation (awakenings during the night; M. L. Chen et al., 2012; Dyląg et al., 2021; Goril et al., 2016; Ipsiroglu et al., 2019; Mughal et al., 2020). In the small PSG study by M. L. Chen et al. (2012), that examined the objective sleep of five children with FASD, they demonstrated higher rates of night-time arousals than previously normed data, at a rate of 11 per hour which was similarly reported by Dyląg et al. (2021). Ipsiroglu et al. (2019) also observed increased hyper-arousability, fragmentation and sleep onset latency (SOL; time taken to fall asleep) using both behavioural video recordings of sleep as well as a very small sample of PSG recordings. Conversely, there are some studies who do not report an increase in awakenings but only see a pattern of delayed sleep onset (Wengel et al., 2011), or evidence of poorer sleep efficiency (SE) and reduced total sleep time (TST; Goril et al., 2016; Mughal et al., 2020). Supporting subjective reports of pathological sleep, PSG data has also revealed that between 50-58% of children could be diagnosed with a sleep disorder such as parasomnias or insomnia compared to a rate of 20-30% in typically developing children (Dyląg et al., 2021; Goril et al., 2016). Additionally, increased rates of disordered breathing during sleep have been observed (M. L. Chen et al., 2012; Dyląg et al., 2021; Ipsiroglu et al., 2019).

There has been little research specifically into the characterisation of SWS in this population and how it may pertain to cognitive deficits. Previous PSG studies on children with FASDs have found no differences in time spent in SWS compared to unexposed children (M. L. Chen et al., 2012; Dyląg et al., 2021). Inkelis and Thomas (2018) reviewed the limited research on infants with PAE, assessing their sleep architecture in comparison to healthy infants. They found that heavier PAE was associated with increased arousals particularly in NREM sleep and difficulty reaching NREM sleep in three-day old infants. Rodent models have also examined the effects of PAE on SWS through exposing mice and rats to ethanol during critical development

stages that are equivalent to the third trimester of human pregnancy. Results indicate a consistent pattern of reduced SWS percentage and cycle length, highly fragmented SWS and higher SWS onset latency (Apuzzo et al., 2020; Lewin et al., 2018; Volgin & Kubin, 2012; D. A. Wilson et al., 2016). Animal and infant evidence does thus far point towards a possible disruption to SWS mechanisms in prenatally exposed brains, although these findings have not been replicated in the few PSG studies in children and have not been investigated in older FASD populations.

Regarding other aspects of SWS quality, despite the importance of SWS-depth and fast spindles as active ingredients in memory consolidation, few to no studies have investigated these phenomena in FASD research. A handful of studies have examined power bands during short (5-10 min) restful waking periods (e.g. Candelaria-Cook et al., 2021) with one study examining overnight sleep, although no differences were found in the delta frequency band between adolescents with FASD and healthy controls (Kaneko et al., 1996). However, some evidence has pointed to altered delta activity during NREM and REM sleep in infants which persisted for six weeks postnatally, resulting in more power across these sleep stages compared to unexposed infants (Inkelis & Thomas, 2018). Nevertheless, it is unclear whether findings derived from infants would be observed in prenatally exposed adults. Lastly, no literature has explored the characterisation of fast spindles in individuals with PAE, despite their connection to consolidation process during SWS.

Given the connection between SWS quality and declarative memory consolidation it is important to explore these features more thoroughly in individuals exposed prenatally to alcohol given their possible role in the memory difficulties they experience. Although current FASD sleep studies crudely show an equivalent duration or proportion of SWS in individuals with PAE in comparison to unexposed individuals, no studies have specifically analysed SWS

characteristics indicative of its quality such as fragmentation, depth and spindles in young adult FASD populations. These are imperative to understand in relation to cognitive outcomes such as declarative memory.

FASD and Memory

Alcohol exposure in utero has been associated with a wide range of adverse cognitive effects including impaired eyeblink conditioning, executive function and spatial memory (Dodge et al., 2020; Jacobson et al., 2008; Kingdon et al., 2016; Mattson et al., 2019). Declarative memory has been found to be particularly vulnerable to PAE from both subjective (Agnihotri et al., 2019) and experimental accounts (du Plooy et al., 2016). Subjectively, children with FASD have reported more difficulties across all memory domains compared to unexposed children in the Everyday Memory Questionnaire (Agnihotri et al., 2019).

Experimentally, children and adolescents exposed prenatally to alcohol show clear immediate and delayed recall deficits as well as difficulties with recognition across the California Verbal Learning Test for Children (CVLT-C), Children's Memory Scale (CMS) and similar tasks (Coles et al., 2011; Crocker et al., 2011; Gross et al., 2018; Lewis et al., 2015; Nardelli et al., 2011; Willoughby et al., 2008). These deficits, related to encoding or ineffective encoding strategies, are also supported by a review of the harmful effects of PAE on the developing brain, including the hippocampus which is crucial for declarative memory encoding (Lebel et al., 2011). Evidence shows that the hippocampus is highly sensitive to PAE, exposure to which results in smaller bilateral or unilateral hippocampi that persist through childhood into adolescence (Coles et al., 2011; Lebel et al., 2011; Nardelli et al., 2011; Willoughby et al., 2008). In addition, these abnormalities have been related to poorer immediate and delayed recall for declarative information in individuals with a FASD diagnosis (Coles et al., 2011; Willoughby et

al., 2008). However, Nardelli et al. (2011) did not report an association between smaller hippocampi and worse narrative memory or memory for names in a neuropsychological battery. Nevertheless, despite some inconsistencies, there is evidence that smaller hippocampi due to PAE, show a pattern of poor encoding of information.

A handful of the declarative memory studies have assessed retention of declarative information over these short delays using an adjustment approach to account for initial or overall learning in children with FASDs (Crocker et al., 2011; Gross et al., 2018; Lewis et al., 2015; Willoughby et al., 2008). Retention is a behavioural measure of the consolidation process, accounting for information lost or gained over a period of time. There have been mixed results concerning impaired retention over short delays with some studies reporting that retention is preserved (Crocker et al., 2011; Lewis et al., 2015) and others highlighting that individuals with FASDs have impaired consolidation even after controlling for IQ and overall learning (Gross et al., 2018; Lewis et al., 2015; Willoughby et al., 2008). For example, Lewis et al. (2015) found that CVLT-C retention differed for two cohorts being assessed, with a sample from Detroit showing impairment while the Cape Town cohort's retention was preserved. They hypothesised that the more moderate exposure in the Detroit cohort allowed them to encode more information, revealing the retention difficulties compared to the heavier exposed Cape Town cohort whereby encoding challenges may have masked problems with retention. Additionally, du Plooy et al. (2016) reported that of the ten studies accounting for declarative memory retention, the majority reported that retention was intact for individuals with PAE. Given that it is uncommon to report retention, no associations have been explored in relation to the hippocampus, which is a crucial brain structure related to encoding as well as consolidating information particularly during sleep-dependent processes.

Scarce research has been done on the relationship between sleep in FASD and cognitive outcomes, with none examining declarative memory. Mughal (2020) and Mughal et al. (2020) explored elements of this relationship across three groups of children, either diagnosed with FASD or autism spectrum disorder (ASD) in comparison to typically developing children. They found that poor sleep quality in those with FASD was significantly associated with poorer attention, working memory, receptive vocabulary and verbal outcomes when compared to typically developing children. However, although this research explored the sleep-cognition relationship it did not examine sleep-dependent consolidation through a measure of retention. Importantly, the current literature has only examined retention over short daytime periods, therefore the reason the majority have observed spared retention may be because consolidation deficits are only or more evident over a sleep period, which is when consolidation primarily occurs, and not during waking.

Rationale and Research Aims

Research into the relationship between SWS architecture, hippocampal volume and neutral declarative memory in individuals with FASD is lacking despite evidence of their sleep disturbances, abnormal hippocampi and memory deficits. There is a vast literature highlighting the importance of SWS macro- and micro-architecture for the consolidation of declarative information. In addition, there is some evidence demonstrating that youth with FASD have potential alterations to their SWS, alongside their established general sleep disruptions. However, these SWS-related disruptions need to be characterised in an adequately powered adult population. Furthermore, prenatally exposed youth are found to have alterations in the hippocampus which have been tentatively associated with their impaired neutral declarative memory, specifically associated with encoding. More research is needed to explore whether

hippocampal-memory performance associations are also specific to consolidation difficulties and whether these are present over a sleep interval, the key period for declarative memory consolidation. Furthermore, it is unclear if these associations are apparent in adulthood, when individuals are expected to manage work and family responsibilities and are, therefore, reliant on intact cognitive functioning.

Given the known role of the hippocampus in consolidation processes, findings of smaller hippocampi in FASD-diagnosed individuals coupled with their potentially altered SWS macro- and/or micro-architecture, it is plausible that these structural and physiological alterations may give rise to the proposed impairments in overnight consolidation. This gap in the literature prompts further research as FASD is a global health concern resulting in adverse and enduring deficits and understanding these relationships may and provide insight to develop intervention strategies targeting sleep, a modifiable biological function, to boost cognition. The proposed study aims to investigate these relationships and provide new insights through the Cape Town Longitudinal Cohort.

I aim to investigate how PAE may be associated with sleep difficulties, that I predict will explain memory performance deficits in this group of individuals. When considering sleep and memory associations in those with PAE, I will take into account existing brain abnormalities which may influence the association, and I will also consider two classifications of in utero alcohol exposure. The first classification takes a diagnostic categorical approach using the classification determined during early childhood (Jacobson et al., 2008). Participants originally enrolled into the cohort were classified as FAS, PFAS, non-dysmorphic heavily exposed (HE) and healthy controls. The second lens takes a continuous PAE measurement approach, obtained through maternal self-report, recording the number of units of absolute alcohol consumed during

pregnancy. When PAE is referred to within this paper it encompasses both classifications and I will specifically refer to FASD diagnostic groups or the continuous measure of PAE, as relevant.

My first aim was to understand how PAE may be related to sleep, hippocampal and memory outcomes, examined through both categorical and continuous lenses. I first intended to characterise and compare SWS characteristics, through objective sleep measures, across FASD diagnostic categories. I also aimed to replicate these between-group differences by examining associations between measures of SWS and alcohol exposure during pregnancy. Similarly, I aimed to establish whether there were between-group differences in, and alcohol exposure-related associations with, hippocampal volumes and memory retention (the percentage of information retained over an 8-hour sleep period). Specifically, I hypothesized that:

1) Individuals with PAE would have:

(a) more SWS disruption characterised by less time spent in SWS, more fragmented SWS, reductions in SWS-depth, and altered fast spindle and coupling properties

(b) smaller childhood hippocampal volumes, and

(c) impaired memory retention.

My second aim was to ascertain which aspects of SWS were meaningful in predicting memory retention. I also aimed to examine the interplay between PAE, hippocampal volume and SWS characteristics in relation to consolidation outcomes. In particular, whether these variables, in concert with each other, influence how information is retained after a sleep period.

I hypothesized that:

2a) SWS associated micro-, macro-architecture or both will predict memory retention.

2b) Individuals with PAE who have smaller hippocampi and SWS-related alterations, will have poor memory retention after a period of sleep.

Methods

Design and settings

The current study uses a cross-sectional case-control design to investigate the associations between SWS parameters, hippocampal volume and neutral declarative memory retention in individuals with and without PAE. This study is nested in a larger research collaboration between UCT and Wayne State University (WSU), spanning a number of decades, since the recruitment of this participant cohort between July 1999 and January 2002 (Biffen et al., 2020; Dodge et al., 2020; Lewis et al., 2015; Meintjes et al., 2014; Jacobson et al., 2021, 2008). Within this research agenda, there is a current parent project that aims to investigate the relationship between sleep architecture, declarative memory and emotion regulation in individuals with and without PAE. This study is distinct from the larger project, because while the larger project investigates broad sleep architectural differences in relation to neuropsychological domains, this study examines only the association between, SWS macro- and micro-architecture, childhood hippocampal volume and memory retention in individuals with and without PAE (Appendix A for a full description of the differences between the parent and current study). Data for the parent study was collected over three nights at the ASCENT sleep laboratory, but only data from night two was reported in this study. With permission, archival hippocampal and intracranial volume (ICV) data of the participants between the ages of 9-11 was also included in the analysis and the data collection, cleaning and analysis processes are outlined in Appendix B (Biffen et al., 2020).

Participants

Participants between the ages of 20-23 were recruited from the Cape Town Longitudinal Cohort by a research nurse between March 2022 and November 2023. This cohort includes

young adults from mothers who (1) engaged in heavy drinking during pregnancy or (2) abstained or drank only minimally. FASD status was confirmed by dysmorphologists in earlier work (Jacobson et al., 2021). In total 87 participants were recruited into the current study. After recruitment, four withdrew (did not return for rescheduling or the initial sleep night) and one participant did not complete experimental night two. A further six were excluded during analysis in accordance with the eligibility criteria for this study (e.g. third trimester pregnancy: $n = 1$, continued or chronic substance use: $n = 3$, shift work: $n = 1$, chronic sleep medication and anti-psychotic use: $n = 1$), leaving a total sample of 76 across the diagnostic categories (FAS/PFAS: $n = 24$, HE: $n = 23$ and controls: $n = 29$). I chose to group the diagnostic categories as FAS/PFAS, HE and controls as the FAS/PFAS group are the most clinically similar in terms of physical growth abnormalities and neuropsychological difficulties. Additionally, isolating the FAS group ($n = 6$) would make it difficult to compare against the larger groupings in the between-group analysis as it has the fewest participants because it is the most severe diagnostic category. It is more appropriate for the HE group to stand alone as the definition of this category is absence of physical features indicative of PAE despite exposure. Thus, this group is distinct from the FAS/PFAS group in terms of being less severely physically affected by PAE.

I conducted a power analysis and calculated an estimate effect size based on previous literature examining sleep disturbances in FASD (Benson et al., 2023; Mughal et al., 2020) and other neurodevelopmental disorders, as studies examining these associations in FASD did not report effect sizes. For the former, studies reported medium to large effects and for the latter, studies indicated small to medium effect sizes (Desaunay et al., 2020, 2023; Mughal et al., 2020; Rochette et al., 2018). Given this, I chose a medium Cohen's $d = .45$. Using this effect size, power = 0.95, $\alpha = .05$ and the maximum number of predictors ($n = 8$) a one-way Analysis of

Variance (ANOVA) required a sample of $n = 81$ and linear regression $n = 59$. These sample sizes are congruent with the parent study's recruitment results.

Eligibility Criteria

See Jacobson et al. (2008) for initial study eligibility criteria. In the current study eligibility criteria were implemented to reduce the number of external factors that may affect SWS architecture, and neutral declarative memory.

1. Participants with neurological conditions other than FASDs (e.g. epilepsy, traumatic brain injury, other neurodevelopmental conditions) were excluded due to their effects on sleep and or memory. Epilepsy has been shown to affect sleep architecture regardless of whether it is controlled with medication, resulting in more fragmented sleep (Tork et al., 2020). Anti-seizure medication can also affect sleep, reducing SWA and decoupling spindles from slow waves, which are pertinent to sleep-dependent memory consolidation (Roebber et al., 2022). Traumatic brain injuries have also been associated with altered sleep architecture, including increased amounts of SWS and overall fragmentation (Mantua et al., 2018; Modarres et al., 2017; Parcell et al., 2008). A range of neurodevelopmental conditions are also associated with a variety of sleep disorders and memory deficits, see Ashworth et al. (2015) as well as Blackmer and Feinstein (2016).

2. Participants who were chronic users, defined as individuals using cocaine, methamphetamine, amphetamine, and/or opiates in a daily or near daily-use pattern were excluded due to the acute, withdrawal and long-term effects of these substances on sleep patterns, especially SWS, and memory (Angarita et al., 2016; Garcia & Salloum, 2015; Gordon, 2019). These individuals were identified using the Timeline Follow-Back Interview (TLFB) on night one or a positive Drugs of Abuse (DOA) test. Participants

who were recreational users, defined as using these substances infrequently, were asked to refrain from using them for seven days before arriving at the sleep laboratory while they were contacted to complete the pre-laboratory sleep diary. A week is enough time for these substances to have been removed from the body for occasional recreational users but not for chronic users (Vandevenne et al., 2000). Only participants reporting recreational use with positive DOA results were given a second chance. They were excluded if they had a second positive DOA test at the later date as the inability to abstain provided evidence of a heavier use pattern.

3. Participants using marijuana, as determined through interviews and a drug screening test detecting the active ingredient tetrahydrocannabinol (THC), were permitted into the study. This was due to the large number of participants using marijuana within the sample. Excluding such participants would have largely and negatively impacted recruitment. Marijuana use has been shown to affect sleep in acute and chronic users. In low to moderate acute doses, it has been seen to decrease SOL and increase SWS percentage (Bolla et al., 2008; Schierenbeck et al., 2008). However, of the limited studies available, chronic use, which is common to the sample, has shown some tolerance effects regarding SWS, with less of an increase in SWS compared to naïve users, although one study also demonstrated a long-term suppression of SWS (Angarita et al., 2016; Babson et al., 2017; Bolla et al., 2008; Schierenbeck et al., 2008). These mixed effects suggest variability in response to THC. Together with the high prevalence of marijuana use and consequent potential restriction on recruitment, I opted to include participants using this substance but recorded their use for covariate analytic purposes.

4. Participants using alcohol regularly were also permitted so as to not limit the already modest sample size. Chronic or heavy use of alcohol is defined as 15 or more drinks in a week for men or eight in a week for women (National Institute of Alcohol Abuse and Alcoholism, 2024), or more than four or five drinks in a day for women and men, respectively. Chronic alcohol use has been shown to affect sleep quality, especially during the first few days of abstinence following periods of drinking. This includes increased SOL, sleep fragmentation, reductions in time spent in SWS and SWS-depth (Angarita et al., 2016). Due to these potential effects on SWS and its effects on memory, use was recorded and included in data analysis.

5. Participants with severe depression and anxiety scores on the Beck Depression Inventory Second Edition (BDI-II) and Beck Anxiety Inventory (BAI) were not excluded. Although these disorders are associated with adverse effects on sleep and memory (Oh et al., 2019; Papadimitriou & Linkowski, 2005), I did not exclude high scoring participants (BDI: n = 7; BAI: n = 3) in order to maintain participant numbers, opting for statistical control instead. Overall, group depression and anxiety scores were minimal to mild (see Table 1).

6. Participants diagnosed with Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) schizophrenia and psychotic, bipolar and other related disorders (American Psychiatric Association, 2013) were not eligible to enrol. These disorders have been associated with poor sleep patterns, including reductions and changes to SWS, spindle density and memory (E. K. Lee & Douglass, 2010; Petit et al., 2022).

7. Participants regularly using medications that aid sleep or may disrupt sleep were excluded.

8. Participants who are within the third trimester of pregnancy were excluded. Sleep architecture and overall quality have been shown to be greatly affected during late pregnancy demonstrating reduced SWS and SWS-depth along with a greater risk of memory deficits (Izci-Balserak et al., 2018; Płotek et al., 2017; D. L. Wilson et al., 2010).

9. Participants who were night-time shift workers were excluded as shift work affects one's natural circadian rhythm, altering normal sleep patterns (Boivin et al., 2021), which results in homeostatically regulated rebound sleep after shiftwork with increased SWS and SWS-depth (Pedersen et al., 2022). Additionally, night-time shift work has been shown to negatively affect a range of cognitive processes in the short and long-term and is associated with sleep-related performance deficits (Ruggiero & Redeker, 2013).

Measures

Sleep Diary

This measure was used to ensure that participants' habitual bedtimes were preserved while at the sleep laboratory as inconsistent bedtimes are associated with poorer sleep quality (Kang & Chen, 2009; Appendix C). The diary was administered telephonically over seven days before the participant arrived at the sleep laboratory and after each night in the lab to ascertain the participant's sleep habits and subjective sleep quality. The measure includes questions such as, "*How long did it take you to fall asleep?*", "*How many times did you wake up, not counting your final awakening?*" and "*How would you rate the quality of your sleep?*" which is accompanied by a 5-point Likert scale from "very bad" to "very good".

DOA Screening Test

The screening measure assessed for the presence cocaine, methamphetamine, amphetamine, marijuana (THC) and opiates in the participants' urine (Appendix D). This was

administered upon arrival for the adaptation night and was used to log substance use, reschedule participants positive for substances other than THC or exclude those unable to cease use at the time of a second rescheduled visit. An online form was used to log when the substance was consumed, how much was consumed and how often the individual uses it.

Demographic measures

A host of demographic measures were administered during the adaptation night to record basic and more nuanced socio-demographic as well as clinical characteristics (Appendix E). Socio-demographic information included, age, sex, employment status, level of education, marital status, health and medication history.

Pittsburgh Sleep Quality Index (PSQI). The PSQI was used in conjunction with the sleep diary as a measure of subjective sleep characteristics (Appendix F). Specifically, it was administered to determine participants' sleep habits and quality in their usual sleep setting over the past month. The PSQI contains 19-self rated questions which are grouped to form seven subcategories (Buysse et al., 1988; Appendix H). Each question is scored from 0-3, and the results are added to produce scores for each category as well as a global PSQI index score ranging from 0-21. A cut-off score of five is indicative of poor sleep, with higher scores reflecting worse sleep quality (Buysse et al., 1988). The self-rated questions determine participants' sleep duration and latency, sleep medication use as well as severity and prevalence of sleep problems over the past month (Buysse et al., 1988). The scale possesses good internal consistency (Cronbach's d = .83; Backhaus et al., 2002; Buysse et al., 1988) and a high test-retest reliability (r = .87; Backhaus et al., 2002). The PSQI is established as a sound and thus valid measure to identify sleep problems as it is clearly able to distinguish between control and insomnia patients (Buysse et al., 1988; Carpenter & Andrykowski, 1998). The PSQI also

displays high convergent validity through strong correlations with well-established measures of the same construct (e.g. Center for Epidemiologic Studies-Depression Scale; $r = .69$; Carpenter & Andrykowski, 1998) and sleep diaries ($r = .71$-$.81$, $p < 0.001$; Backhaus et al., 2002) while divergent validity was evident with poor correlations to unrelated constructs (e.g. Profile of Mood States; $r = .37$). Studies exploring the sleep quality of individuals with neurodevelopmental disorders such as ASD and ADHD have also used the PSQI and highlighted its ability to distinguish neurodivergent from neurotypical individuals through sleep quality. For example, those with ASD and ADHD score significantly higher globally and across certain sub-categories (Çelikkol Sadiç et al., 2024; McLean et al., 2021) than control participants. Hence, it is likely that the PSQI is appropriate for use.

Hollingshead Four Factor Index of Socio-Economic Status. The Hollingshead Scale was used to calculate the socio-economic status (SES) of participants (Hollingshead, 2011). The calculation uses level of education (rated 1-7; depending on years of education obtained) and occupation rating (rated 0-9; depending on employment and type, with 0 indicating unemployment) in the equation and the output totals are categorised from the lowest social strata (Tier 1) to the highest (Tier 5). This scale has been previously used within the sample (Dodge et al., 2020).

TLFB for Alcohol and Drug Use. The TLFB (Sobell & Sobell, 1995) was administered to estimate drinking and substance use habits over varying lengths of time (Appendix G). Previously the measure was used to ascertain drinking patterns during pregnancy to derive maternal reports of alcohol use such as ounces of absolute alcohol per drinking day across pregnancy (AA/dd; Jacobson et al., 2008). For current participants the interview was administered during the adaptation night to ascertain drinking and substance use patterns over

the past month. Alcohol use was determined by asking participants which days they drank over the past week, two weeks and four weeks. For each drinking day participants were asked questions such as "*what type and brand of alcohol did you drink*", "*was the alcohol shared and between how many?*" and "*how much did you drink?*". Volume of alcohol consumed was recorded and converted to ounces of absolute alcohol (AA) using multipliers proposed by Bowman et al. (1975) for liquor (0.40), beer (0.05), and wine (0.12; Dodge et al., 2020). Summary measures were generated, for AA and number of drinking days (DD) over the last week, two weeks and month. Participants were also asked about their smoking habits (including vaping), and how many days per week over the past two weeks they used heroin, cocaine, marijuana, tranquilisers, tik, antidepressants or other drugs. Studies show the TLFB interview to be both a reliable and valid measure of alcohol consumption across contexts and patient groups (Annis et al., 1996; Carey, 1997; Sobell et al., 2001). This interview method has been previously used and seen as a reliable and valid measure within the South African context and this population (Jacobson et al., 2008, 2018; May et al., 2013; Viljoen et al., 2005).

BDI-II. The BDI-II was chosen to evaluate the severity of depression amongst our participants (Appendix H). The self-report measure, developed for adolescent and adults, consists of 21-items each rated using a 4-point Likert scale, where one selects the statement best describing their mood during the past two weeks (Beck et al., 1996). Higher scores are indicative of more depressive symptomatology with a score of 29 and above classified as severe. The instrument has a high internal consistency reliability (Cronbach's a = .92, .90) and test-retest reliability ranging between r = .73-.96 (Beck et al., 1996; Y. P. Wang & Gorenstein, 2013). The BDI-II has also shown reliability as a research tool within South African populations

(Cronbach's *a* = .90; Kagee et al., 2014; Mendham et al., 2021; Rousseau et al., 2021; C. L. Ward et al., 2003).

BAI. The BAI was chosen to evaluate the severity of anxiety symptoms for participants over the past month (Beck et al., 1988; Appendix I). The self-report measure consists of 21-items each rated using a 4-point Likert scale rated from '*Not at all*' to '*Severely - It bothered me a lot*'. Higher scores indicate more anxiety symptomatology with a score of 36 and above being categorised as severe. The BAI has high internal consistency reliability (Cronbach's *a* = .92, .94) and moderate test-retest reliability (*r* = .75, .67) with robust convergent validity in relation to the State Trait Anxiety Inventory and Diary Anxiety (Beck et al., 1988; Fydrich et al., 1992). This measure has also been assessed for reliability and been used as a research tool within the South African context (Kagee et al., 2014).

Stanford Sleepiness Scale (SSS)

This measure was used to ascertain subjective levels of alertness at a fixed moment in time prior to administering the nighttime and morning cognitive tasks (Shahid et al., 2012; Appendix J). The scale consists of one item with seven statements, prompting one to choose the statement best representing their perceived level of sleepiness at that moment. The scale is then scored from one (lowest level of alertness; "*Asleep*") to seven (highest level of alertness; "*Feeling active, vital, alert, or wide awake*") and can be compared across different points of a study. The scale has been shown to be reliable and valid, in predicting performance for alertness-based tasks (Broughton, 1982; Hoddes et al., 1973).

Wide Range Assessment of Memory and Learning, Second Edition (WRAML-II)

This measure was used to assess memory performance (Bigler & Adams, 2001; Appendix K). In this study the subtests of story memory (verbal index) and verbal learning (learning index)

were used and were translated into Afrikaans by a Clinical Psychologist whose first language is Afrikaans. A behavioural measure of consolidation was generated for each of the two tasks to determine the retention of information after a sleep-filled delay. This was calculated as a percentage using post-sleep recall performance divided by pre-sleep recall performance for two stories and the last learning trial of a list learning task. The WRAML-II has high internal consistency reliability with coefficient alpha between .80-.89 for story memory and verbal learning (Sheslow & Adams, 1990; Strauss et al., 2006). The WRAML-II also exhibits high criterion and convergent validity as it correlates strongly with other established memory tests such as the Stanford–Binet–Fourth Edition and Wechsler Memory Scale-Revised yielding results between .80 and .72 (Scheffler, 1999; Sheslow & Adams, 1990). The WRAML-II has also been used in South African studies and in studies with individuals with FASDs (Kully-Martens et al., 2022; Lewis et al., 2015; Willford et al., 2004).

PSG Equipment

Two 16-channel Nihon Kohden NeuroFax EEG9000 designed for use in sleep research were used to objectively characterise the participants' overnight sleep. To determine different sleep stages, the study collected bilateral electrooculography (EOG), electrocardiography (ECG) and electromyography (EMG) to monitor eye muscle movement, heart activity and muscle tone, respectively. Ten electroencephalography (EEG) electrodes, measuring brain activity at a 200-Hz sampling frequency, were placed in accordance with the internationally accepted 10-20 system (Jasper, 1958). A bipolar longitudinal montage was used for the digital PSG display including derivations F3-C3, C3-P3, P3-O1 and F4-C4, C4-P4, P4-O2 with referential montage derivations using the ear electrodes (A1 and A2), F3-A2, C3-A2, O1-A2 and F4-A1, C4-A1, O2-A1 (Lipinska, 2016). The American Clinical Neurophysiology Society recommends the use of

multiple montage classes for EEG recordings (Acharya & Acharya, 2019). Standardised filters for recording sleep were employed to ensure integrity of the signal and included an EEG notch filter for electrical line noise (60Hz) and filters for the EOG (0.5-35Hz), EMG (10-70Hz) and ECG (1-70Hz).

Procedure

A research nurse recruited participants from the Cape Town Longitudinal Cohort via cell phone or visiting their last known address. All participants gave consent to be contacted for follow-up during earlier studies conducted with this cohort. Seven days prior to attending the sleep laboratory, participants were given a phone so that they could be reliably contacted to record their sleep diary data. Verbal consent was obtained at this time. They were also reminded not to nap, consume caffeine or partake in extreme exercise before coming to the laboratory. A staff driver then transported the participant to and from the ASCENT laboratory over the three consecutive nights of the study. Participants were provided with basic sanitary items and meals. Assessments were conducted in either English or Afrikaans, based on the participant's primary schooling language and were recorded using Research Electronic Data Capture. Informed consent was obtained from the participants upon their first arrival at the laboratory. A DOA screening test was then administered and if any drug other than marijuana was detected, the participant was asked to reschedule and refrain from using before their next date. Following this, demographic and clinical questionnaires were administered by a research assistant. PSG recordings were conducted at the ASCENT Sleep Sciences laboratory at UCT's Department of Psychology. The first night allowed for acclimation to the PSG equipment. For night two, participants arrived around 6pm and were provided with dinner and thereafter completed the immediate recall of the WRAML-II story and verbal learning subtests. In the story subtest, the

participant was read two paragraph stories and after each one, was given a free recall opportunity and information was recorded and transcribed verbatim. For the verbal learning subtest, a list of the same 16 simple, everyday words were read to the participant over four trials each with a free recall opportunity. Attachment of the PSG was timed to be complete by the participants' usual bedtime, and they were woken after eight hours of overnight sleep. After breakfast participants completed both the delayed free recall and recognition trials of the WRAML-II story task and delayed free recall trial of the verbal learning task whereby intrusions and repetitions were recorded. Thereafter they showered and were transported home or to work.

Ethical Considerations

Ethical approval for the study was granted by the relevant review boards at UCT and WSU (PSY2022-042; HREC 525/2021) and all participants completed informed consent before starting the study (Appendix L). Verbal consent was obtained prior to administering the sleep diary. The informed consent document clearly outlined the procedure, potential risks and benefits, and their right to withdraw from the study without consequence. Participants were also made aware that their information would remain confidential, there were no foreseen harmful consequences of the lab procedures and that they would be compensated for the three nights spent in the lab. They were also made aware that they may request a referral for remedial, medical or social services through research assistants or Principal Investigators.

Statistical Analysis

Before statistical analysis was performed on the EEG data, I, along with another researcher (both accredited AASM PSG coders), scored the overnight PSG data in accordance with the 2023 AASM sleep scoring guidelines (Troester et al., 2023). As independent coders we were blinded to the participant FASD diagnostic category so as not to introduce bias during any

scoring stage. Inter-rater reliability was established at ~89% across all records. Where there were significant discrepancies between scored epochs, these were discussed and re-evaluated to come to an agreement.

Sleep Staging

PSG recordings were exported from Polysmith (Nihon Kohden, Tokyo, Japan) into European Data Format (EDF) files and uploaded into MATLAB (The MathWorks Inc, 2024) to be scored and analysed using scripts from '*EEGLAB*' and '*Danalyzer*' packages (Denis et al., 2021a). Standard sleep stages were scored (W, N1, N2, SWS, REM) to attain stage minutes and percentages. Arousals were also scored and separated into two categories. The AASM Manual defines arousals as periods of abrupt shifts in EEG activity lasting between three and ten seconds, with at least ten seconds between them (Troester et al., 2023). Arousals with a lightening of sleep (LOS) were arousals that resulted in a sleep stage shift to N1 or W and those without LOS (termed Arousals) were those that did not alter the current sleep stage. This allowed for the computation of SWS fragmentation as well as fragmentation over the entire sleep period and other stage-specific fragmentation. Other sleep variables included TST, time in bed (TIB), wake after sleep onset (WASO), SOL, SE, REM latency and Arousal Index (AI). Additionally, the number of awakenings (number of separate periods scored as wake) in total and per sleep stage were included.

Artifact Rejection

EDF files were filtered through a 35 Hz notch filter and .3-35 Hz bandpass filter to reduce artifacts. Artifacts are recorded activity not representative of electrical activity arising from the brain and can be extra-physiologic (e.g., electrical line noise) or physiologic (e.g. sweat, movement). SWS epochs underwent automated artifact rejection (Denis et al., 2021b). This was

achieved through generating Hjorth parameters for each electrode channel per epoch and those containing channels with parameters more than three standard deviations from any parameter means were labelled as artifact and removed (Denis et al., 2021b; Purcell et al., 2017). This was to ensure that only signals indicative of sleep was processed without disturbance from movement or awakening that may create points of outlying signal not representative of SWS.

PSD

I used PSD (uV^2 / Hz) instead of raw EEG power (uV^2) to allow for more reliable inter-individual comparisons (Cox & Fell, 2020; Cunningham et al., 2021; Denis et al., 2021b). This is because frequency resolution for Fast Fourier Transforms (FFT) depends on the length of the signal, thus participants with slightly different lengths of sleep would have varying frequency resolutions. PSD normalises the power per frequency unit to overcome inter-participant differences. PSD was estimated through Welch's method which accounts for the FFT assumption that signals do not change over time. This method deals with the assumption through selecting five second segments of signal using 50% overlapping Hamming windows that are averaged together to obtain an estimate of SWS PSD (Cox et al., 2017; Denis et al., 2021b). In order to counteract the natural 1/f scaling of raw PSD EEG data, which enhances the lower frequencies and tapers off quickly at higher frequencies (Cox & Fell, 2020), PSD was calculated on the derivative of the EEG time series to better understand peaks in the PSD data (Cox et al., 2017; Cunningham et al., 2021; Denis et al., 2021b). Finally, PSD was normalised to the individual, known as relative PSD, by dividing the power at each frequency between 0-30Hz by the average power in that range (Cox & Fell, 2020; Denis et al., 2021b). This is to account for individual variation in EEG signal due to skull thickness, gyral folding and/or electrode positioning (Cox & Fell, 2020). PSD was then averaged across the two frontal channels to gain a measure of frontal

PSD activity for each band, unless recording quality was poor for one, in which case only the preserved channel was used. Relative PSD estimates were generated for each band namely, SO (.5-1.25Hz), delta (1-4Hz) and SWA (.5-4Hz).

Automated Spindle and SO Detection

Fast spindles and SOs were automatically detected using a validated complex Morlet wavelet detector in artifact free SWS epochs (Denis et al., 2021a, 2021b; Mylonas et al., 2020). This method has been shown to improve upon visual inspection to count spindles (Warby et al., 2014). The wavelet half bandwidth was set at 1.5Hz which denotes the frequency width around the peak frequency to detect spindles. Following methods used by Cunningham et al. (2021) and Denis et al. (2021a, 2021b) I determined individualised fast spindle peak frequencies to set in the detector for each participant. Visual examination of the SWS power spectrum was performed to determine the most prominent fast spindle (12.5-16Hz) PSD peak. If a peak was not discernible, it was set at 14Hz (Purcell et al., 2017). A lack of peak in the power spectrum is not indicative of an absence of spindle activity but rather may not be discernible due to the oscillation being infrequent (Cox & Fell, 2020). A spindle was detected when it surpassed six times the median SWS PSD and remained above this threshold for 400ms or longer (Denis et al., 2021a; Djonlagic et al., 2021). These parameters are found to be the most ideal for categorising and capturing spindles across types (Djonlagic et al., 2021). For the fast spindle analysis, activity from the central electrodes were averaged together. I extracted parameters of density (spindles per minute), duration, peak frequency, amplitude and sigma power.

SOs were detected through filtering the signal in the SO band (.5-1.25Hz). All positive to negative amplitude crossings were marked and those where the time between two crossings was

.8-2 seconds were considered. Only the 25% largest amplitude waves were retained as SOs over 300uV were excluded as artifact (Helfrich et al., 2018; Staresina et al., 2015).

SO-Spindle Coupling. SO-spindle coupling was determined using the previously filtered fast spindle and SO signals. A Hilbert transform was then applied to acquire the phase of the SO signal and peak amplitude of the spindle signal (Denis et al., 2021a). Peak amplitude was established for each spindle and whether it occurred during a detected SO. If so, the phase angle of the SO at the spindle peak was calculated. The phase of the delta signal is calculated in radians and can be converted to degrees. A phase of 0° relates to the positive peak of the SO and 180° to the trough. Extracted parameters included coupling percentage (number of spindles coupled to SOs/ number of total spindles), peak phase (average phase of SO that coupling occurred) and peak strength (a measure of coupling consistency where 0 indicates that coupled spindles never occurred at the same phase of the SO and 1 indicating perfect precision in phase across coupled spindles). The central electrodes were used for this analysis.

Statistical Analysis for Hypotheses

Descriptive and inferential statistical analysis were conducted using RStudio version 4.3.1 (RStudio Team, 2024). Statistical significance was set at $a = .05$. I compiled the descriptive statistics to compare FAS/PFAS, HE and control groups. Several minor adjustments were conducted on the data. The hippocampal data had some missing movement-corrected data. For those cases ($n = 4$), non-movement corrected data was used. In a previous analysis by Biffen et al. (2020) it was found that the movement compared to non-movement corrected measurements were highly correlated ($r = .80$). As a result, inserting the four missing data points were unlikely to be problematic.

Before embarking on hypothesis testing, I evaluated the sample characteristics. I examined whether there were significant differences in any sample characteristics and whether they were associated with PAE or memory retention using Pearson and Spearman correlations. This was to determine any potential variables that would need to be included within subsequent analyses to control for their potential impact. I assessed age, sex, SES, depression, anxiety, ICV, alertness, substance use and pre-laboratory subjective sleep measures using T-tests, Chi-Squared analyses, one-way ANOVAs, or Kruskal-Wallis rank sum tests if ANOVA assumptions were violated.

Hypothesis 1 Analysis. Before starting my analysis to determine whether those with PAE have altered SWS, reduced hippocampal volumes and worse neutral declarative memory retention compared to those with mild or no exposure, I first assessed the assumptions of ANOVA. Observations were independent and normality was statistically computed using the Shapiro-Wilk test and visually assessed through histograms. Homogeneity of variance was assessed using Levene's test. I then conducted the between-group analysis with regards to variables related to SWS, hippocampal volume and story and word-list retention. I chose to average the results from the two stories of the WRAML-II to provide a combined score reflective of the story subtest and to lessen the number of variables in the analysis.

Due to the large number of SWS variables, I selected a few for my analysis. This is to minimise the number of correlations one would need to correct for to account for inflated type 1 error. I chose SWS minutes and percentage which represent SWS macro-architecture, both SWS arousal types, SWS PSD for each of the three bands and only fast spindle coupling parameters. I chose not to include fast spindle parameters as it is the timing of SWS oscillations, reflected in the coupling process, which is the most crucial for the consolidation of information during sleep

(Klinzing et al., 2019; Ng et al., 2024). Additionally, due to their association with PAE as well as the relationship between poorer, more fragmented sleep and worse outcomes related to consolidation I included SWS arousals (M. L. Chen et al., 2012; Djonlagic et al., 2021; Dyląg et al., 2021). Time spent in SWS and PSD were included due to their known or suspected differences in individuals with PAE and relation to memory consolidation processes (Apuzzo et al., 2020; Inkelis & Thomas, 2018).

Most variables central to the hypothesis violated the assumption of normality to varying degrees, except for SWS minutes and percentage as well as delta and SWA PSD. For those variables that did not pass the Shapiro-Wilk test, I visually assessed their distributions using histograms to determine if the violation was mild or severe. From this assessment those with mild violations included story and list retention as well as left hippocampal volume. Levene's test revealed that all variables met the assumption of homogeneity of variance. For those variables with severe violations to normality I used Kruskal-Wallis Rank Sum tests as a suitable non-parametric alternative to the One-way ANOVA as it is robust against outliers, variance and non-normally distributed data (Habibzadeh, 2024). This method was chosen instead of transforming the data, to preserve clarity in the interpretation of the results.

I retained the One-way ANOVA for variables that met the assumptions or to which there were only mild deviations in normality as it is robust against these (Schmider et al., 2010). Eta squared effect sizes were calculated for each variable. Significant between-group ANOVAs and Kruskal-Wallis tests underwent either post-hoc Tukey HSD or Dunn comparisons with Bonferroni corrections to establish where significant differences were observed.

For all significant between-group results, outliers were examined. For those with influential outliers (≥ 3 standard deviations above or below the mean), two comparison tests

were created against the original, one with the outlier(s) removed and one with a winsorised version of the variable. Winsorising aims to reduce the influence of outliers by limiting all extreme values and bringing them nearer to the distribution of the other data points (Abuzaid & Alkronz, 2024). In this case I chose a percentile cutoff below 5% and above 95% which replaces values below or above those extremes of the distribution with the 5 and 95 percentile values, respectively. The mean is altered while the median remains unchanged and unlike outlier removal, all data points are retained. If neither comparison test differed from the original, the original analysis was retained. If the comparisons did differ, the best option was chosen for the data.

Outliers were found for left and right hippocampal data as well as story retention. For the analysis related to left hippocampal volume, the winsorised version of the variable was retained as it improved the overall ANOVA significance as well as uncovered an additional significant post-hoc comparison. Right hippocampal volume and story retention remained as the original variable as the comparison analyses without the outliers did not differ from the original analyses.

Analyses of covariance (ANCOVAs) were then performed for any SWS, hippocampal or retention variables that met assumptions for ANOVA and were associated with any sample characteristics. This was to determine the effect of the sample characteristic in terms of whether it rendered between-group differences non-significant, thus indicating that the characteristic has a larger effect and more explanatory power for the particular outcome variable in comparison to PAE. ICV and sex were included for hippocampal volume and sex, SES and current cigarette use for story retention. It is imperative to control for ICV when examining regional specific brain regions to account for individual variation in head size (O'Brien et al., 2006; J. Wang et al., 2024). Thus, even though ICV was not associated with hippocampal volume it was included

using an adjustment approach to make accurate observations about hippocampal volume across groups (J. Wang et al., 2024). Sex is also an important variable to account for as individuals identifying as male tend to have larger total and regional brain areas, such as the hippocampus, in comparison to those identifying as female (Ruigrok et al., 2014).

While the ANOVA and ANCOVA analyses explored between-group differences based on FASD diagnostic criteria, I also evaluated the associations between a continuous measure of in utero alcohol exposure (AA/dd) and SWS-related variables, hippocampal volume and memory retention using Spearman correlations. Chosen SWS variables were identical to the between-group analysis. Spearman correlations were performed due to the skew nature of the maternal self-report PAE variable, as most mothers report zero to very few drinks across pregnancy, with a smaller percentage reporting a higher amount. P-values were adjusted for the multiple correlations using the Benjamini-Hochberg procedure to avoid type 1 errors.

Hypothesis 2 Analysis. My second aim was to determine whether PAE, hippocampal volume and SWS interact to influence memory retention. Before starting the regression analysis, I first determined whether there were significant Spearman and Pearson associations with story and list learning retention to SWS macro- and micro-architecture variables. This was to determine which sleep variables, if any, were related to these memory outcomes and to limit the number of SWS-related variables in the model-building process. Significant associations were chosen as the SWS moderators whose ability to predict retention, independently and through interactions, would be assessed.

Separate analyses were completed for the dependent variables, story and verbal learning (word-list) retention. For each retention variable separate sets of models were created assessing PAE with either FASD diagnostic group or AA/dd as predictors. For models assessing either

diagnostic or continuous measures of in utero alcohol exposure, separate models were created to assess each significant SWS variable that correlation analyses showed were associated with the consolidation processes. When creating the linear regression models, I first assessed the three-way interaction (SWS*PAE*Hippocampus) for each model creating one for left and right hippocampal volume, if it was not significant, I then examined for two-way interactions between SWS and either PAE or hippocampal volume. The analyses did not include PAE-hippocampal interactions, because the overall aim of the study focused on the role of sleep in memory consolidation for individuals with PAE. The chosen two-way interactions were to determine whether SWS was moderating the relationship between PAE and/or hippocampal volume and memory retention, because SWS may moderate only one factor, without the interaction of all three variables.

Significant interactions were examined further, while models without interactions were simplified to examine only the main effects of the three variables. Variables without main effects in this scenario were not retained in the model-building process. As each model was formed around the chosen SWS variable the analysis was ceased for those that failed regarding moderation effects together with a lack of independent effects.

Models containing interactions and SWS variables with main effects underwent an iterative process of adding covariates previously identified during the analysis of sample characteristics that revealed between-group differences or associations with AA/dd or retention. Using the additive approach, I could assess the impact of each covariate individually and remove it before adding the next one if it was not significant. This reduces the problem of adding too many covariates at once, with the maximum number of covariates in a model at one time being eight. Covariates were retained if they had significant main effects and improved the overall

model by contributing to variance explained. If a covariate was only trend-level its effect size, and standardised beta-coefficients were also evaluated. I assessed all covariates and only stopped adding them to the model if the addition of one negated the interaction or main effects of any central variable and this was noted.

Only variables predictive of memory retention were retained for each model and eta squared effect sizes were calculated. Where significant interactions were observed I performed additional slope analyses and generated visual representations of the interactions to better understand the influence of SWS on the relationship between PAE, hippocampal volume and memory retention.

Residuals and outliers more than or equal to three standard deviations above or below the mean were assessed across all models. Residuals were normally distributed or had only mild deviations in their distributions across all models. In support of this Breusch-Pagan tests also revealed that all models were homoscedastic. Some influential outlying points were found to be similar across multiple models. They were removed and the new models were compared to their original counterpart. The influence of their removal was inconsistent with some resulting in improved and others in poorer models despite being the same outlying point. Nevertheless, these points are still representative of the actual observations in the sample (rather than being erroneous) and were not harmful to the model with regards to residuals and their distribution and spread. For these reasons I retained them within the analysis. Twelve models were created, however, only five have been discussed with the others added as Supplementary material (Appendix O, Appendix P).

Results

Sample Characteristics

Both tables 1 and 2 show information about the demographic characteristics, PAE, presence of mood disturbances, substance use and general sleep quality within the sample.

Participants in this cohort were young adults with a mean age of 21.68 years old. They were matched in terms of sex both within ($X^2(1) = 0.803$, $p = .370$; $X^2(1) = 1.815$, $p = .177$; $X^2(1) = 0.032$, $p = .856$) and between-groups as well as with regards to continuous alcohol exposure ($W = 740$, $p = .847$). Regarding SES, most participants came from a lower SES background with scores representing a combination of an individual's level of education and occupation. As expected, individuals diagnosed with FAS/PFAS had the highest rates of PAE, as measured through AA/dd, compared to HE and control individuals. Those in the FAS/PFAS group were exposed the highest ounces of absolute alcohol per drinking day during pregnancy while individuals in the HE group had a lower exposure. Controls, as expected, were very minimally exposed. BDI-II and BAI scores for the sample were similar across diagnostic groups on the border of minimal and mild symptoms of depression ($M_{sample} = 14.46$) and mild regarding symptoms of anxiety ($M_{sample} = 10.54$).

In comparison to normative samples, ICV fell just below the normative ranges for children between the ages of eight and ten reported by Satanin et al. (2024). While normative data suggests that males should have a volume of 1448.5cm^3 and females 1373.4cm^3 on average (Satanin et al., 2024) the sample mean was only 1296.105cm^3. Nevertheless, the ICV was similar across groups.

Levels of alertness before memory testing, measured through the SSS, were between 5.5 and 6.5 out of a total of seven indicating a high level of alertness for both assessment times.

Alertness levels were consistent within groups for nighttime and morning assessments (t (23) = 0.548, p = .588; t (22) = 0.900, p = .377; t (28) = -1.045, p = .304), and fell below conventional levels of significance between-groups.

As for substance use, there was only one participant using either tik or tranquilisers, in non-heavy use patterns. Marijuana consumption on the other hand was high (n = 30) and (n = 21) displayed a heavy, daily-use pattern. On average participants consumed the substance on 4.41 days over the past two weeks and this pattern of use did not differ across diagnostic groups. Alcohol and cigarettes were widely consumed by the sample and use of these substances was uniform across the groups.

General Sleep Characteristics

The subjective sleep habits of participants prior to arriving at the sleep laboratory are presented in Table 2. The results from the PSQI indicated that participants' scores, on average fell above the cut-off score of five (M_{sample} = 5.72), indicating poor sleep quality across the sample. Participants' subjective sleep reports, garnered from the sleep diary administered the week before testing, showed an average SE of M_{sample} = 84.45%, which improved somewhat when participants slept in the sleep lab during the adaptation night, M_{sample} = 90.33%. Average subjective sleep quality prior to arriving at the sleep laboratory was rated as "OKAY" per the Likert scale (M_{sample} = 3.48), along the spectrum of ratings from 1-5 corresponding to very bad to very good sleep quality.

Objective sleep patterns were highly similar across groups (see Table 2). Normative values for healthy individuals between 21-30 years old have been taken from Bonnet and Arand (2007; macro-architecture), Iskander et al. (2023; SOL). On average participants took 21.18

Table 1

Descriptive Statistics and Between-Group Differences of the Sample Characteristics (N = 76)

	Group					
Variable	Control (n = 29)	HE (n = 23)	FAS/PFAS (n = 24)	F/X^2	p	*ESE*
Age	21.90 (0.67)	21.45 (0.74)	21.62 (0.58)	2.89	.06	.07
Sex				2.780	.249	.10
Female	15	8	14			
Male	14	15	10			
SES	25.14 (7.51)	23.63 (7.56)	17.52 (5.22)	8.670	<.001***	.19
AA/dd	0.04 (0.24)	3.11 (1.51)	4.35 (2.05)	58.40	<.001***	.77
BDI-II	13.86 (12.53)	15.70 (9.35)	14 (9.93)	1.618	.445	.00
BAI	10.72 (12.38)	11.30 (7.40)	9.58 (10.06)	2.473	.290	.00
ICV	1274.14 (162.25)	1336.07 (118.78)	1283.26 (137.81)	1.281	.284	.04
SSS_{Night}	5.69 (1.47)	5.83 (1.11)	6.46 (0.83)	5.587	.061	.04
$SSS_{Morning}$	5.93 (1.28)	5.57 (1.16)	6.33 (0.87)	5.53	.063	.04
Marijuana	3.29 (5.85)	5.96 (6.75)	4.25 (6.05)	2.767	.251	.01
Cigarettes	4.13 (3.99)	6.21 (4.85)	5.69 (5.60)	2.341	.310	.00
Tik	0.00 (0)	0.00 (0)	0.17 (0.82)	2.125	.346	.00
Tranquilisers	0.00 (0)	0.17 (0.83)	0.00 (0)	2.261	.323	.00
DD Week	0.36 (0.56)	0.52 (0.67)	0.54 (0.66)	1.321	.517	.00
DD Two Week	0.89 (1.26)	1.17 (1.34)	0.83 (0.92)	0.817	.665	.00
DD Month	1.50 (2.38)	2.00 (2.00)	1.08 (1.14)	2.777	.249	.01
AA Week	1.42 (2.61)	2.30 (3.98)	2.15 (3.22)	0.988	.610	.00
AA Two Week	2.74 (4.51)	6.22 (9.23)	3.11 (4.35)	1.497	.473	.00
AA Month	5.53 (10.45)	10.41 (14.41)	4.14 (5.50)	3.668	.159	.02

Note. Means are presented with standard deviations in parentheses. SES = Socio-economic status (determined through Hollingshead Index); AA/dd = Units of absolute alcohol consumed per drinking day during pregnancy; BDI-II = Beck Depression Inventory second edition; BAI = Beck Anxiety Inventory; ICV = Intracranial volume in cm^3; SSS = Standford Sleepiness Scale; DD Week = Drinking days over the past week; DD Two Week = Drinking days over the past two weeks; DD Month = Drinking days over the past month; AA Week = Units of absolute alcohol consumed over the past week; AA Two Week = Units of absolute alcohol consumed over the past two weeks; AA Month = Units of absolute alcohol consumed over the past month. ESE = Effect Size Estimate; Cramer's V used for Sex, Eta^2 used for all other variables. $^{***}p < .001$.

minutes to fall asleep, which is double the sleep latency usually observed for this age group. The sample had moderately high SE (M_{sample} = 86.02%) which echoed that of their subjective accounts, although, it was less than what is reported generally in healthy individuals of the same age range. The mean WASO for the sample was 45.12 minutes and the percentage of time spent in Wake was 13.98%. Participants spent double the amount of time in N1 (M_{sample} = 18.74%), less time in N2 sleep (M_{sample} = 37.99%) and slightly more time in SWS (M_{sample} = 16.02%) than what is normally observed. REM sleep and REM latency sample means were lower than normal at 13.19% and 95.06 minutes respectively, indicating participants spent less time in REM and entered REM more quickly than healthy individuals of the same age.

Arousals within this sample were higher than expected as they accrued a high arousal index of 21.28 indicating the number of arousals per hour of sleep. This is double the normally observed values for arousal indices. Regarding each sleep stage participants had more arousals without LOS during N1 sleep, followed by N2, REM and finally, SWS. Arousals with LOS followed a similar pattern although N2 sleep contained the highest number of arousals followed by N1, REM and SWS. The arousal data suggests that the sample had highly fragmented sleep.

Sleep Micro-architecture

Table 3 shows the between-group differences in SWS micro-architecture, which encompasses PSD and spindle architecture. The relative SO, delta and SWA PSD were similar across groups (M_{sample} = 2.12; 2.4; 2.35) with delta and SWA being closer due to overlapping parameters. The lower SO PSD, indicated that within the sample the slowest proportion of SWS waves have a lower amplitude than the delta and SWA PSD bands that include a higher frequency range. Thus, the waves within the 1-4Hz range, included in the delta and SWA bands, seem to have a higher amplitude than those in the .5-1Hz range.

Table 2

Descriptive Characteristics and Between-Group Comparisons of Subjective and Objective Macro- and Micro-architecture of Sleep (N = 76)

	Group						
	Control	HE	FAS/PFAS				
Variable	(*n* = 29)	(*n* = 23)	(*n* = 24)	*norm*	F/X^2	*p*	Eta^2
PSQI Global	5.45 (2.69)	5.22 (2.47)	6.54 (3.86)		1.163	.558	.00
Ave SQ Pre	3.70 (0.58)	3.47 (0.71)	3.20 (0.81)		3.22	.046*	.08
Ave SE Pre	85.33 (9.36)	85.42 (7.20)	82.40 (12.16)		0.756	.473	.02
Ave SQ Night 1	3.36 (0.95)	3.75 (0.58)	3.62 (0.92)		1.023	.366	.04
Ave SE Night 1	90.49 (5.43)	89.75 (6.59)	90.28 (7.68)		0.059	.942	.00
TST	415.34 (39.43)	414.80 (36.42)	416.31 (41.99)	446	0.071	.965	.00
TIB	484.60 (10.24)	483.27 (18.10)	481.79 (11.48)	480	0.149	.927	.00
SOL	19.91 (14.08)	21.43 (22.05)	22.48 (23.92)	11.7	0.448	.799	.00
SE	85.72 (8.03)	85.88 (7.43)	86.51 (9.32)	94.6	0.948	.622	.00
WASO	47.41 (39.11)	44.77 (24.81)	42.67 (31.59)		0.283	.868	.00
Wake (min)	69.26 (38.91)	68.48 (36.15)	65.48 (46.71)		0.927	.628	.00
Wake %	14.29 (8.03)	14.12 (7.43)	13.49 (9.32)		0.948	.622	.00
N1 (min)	93.67 (29.19)	84.73 (27.19)	91.81 (27.75)		0.67	.514	.02
N1 %	19.35 (6.07)	17.55 (5.71)	19.09 (5.81)	9	0.64	.528	.02
N2 (min)	182.83 (35.40)	189.32 (36.84)	179.02 (29.55)		0.53	.589	.01
N2 %	37.72 (7.19)	39.21(7.70)	37.21 (6.35)	54	0.49	.613	.01
SWS (min)	81.02 (27.58)	71.30 (30.45)	79.79 (32.30)		0.74	.482	.02
SWS %	16.71 (5.66)	14.76 (6.30)	16.59 (6.79)	13	0.73	.487	.02
REM (min)	57.83 (21.34)	69.45 (21.40)	65.69 (15.67)		2.34	.103	.06
REM %	11.94 (4.41)	14.36 (4.36)	13.63 (3.22)	19	2.44	.094	.06
REM Latency	106.19 (54.36)	89.18 (35.33)	87.00 (55.06)	125	1.952	.376	.00

Awakenings	38.76 (13.07)	40.77 (15.05)	36.29 (12.98)	22.9	1.477	.477	.00
Arousal Index	21.12 (6.14)	21.20 (6.27)	21.54 (7.04)	10.8	0.01	.994	.00
Arousals Total	84.48 (29.33)	81.14 (28.31)	86.92 (23.85)	83	0.602	.740	.00
Arousals N1	48.72 (25.25)	43.23 (19.55)	46.67 (14.94)		0.985	.611	.00
Arousals N2	21.55 (9.22)	20.95 (6.83)	22.58 (7.87)		0.533	.766	.00
Arousals SWS	2.93 (2.96)	3.59 (2.11)	5.17 (3.21)		7.537	.023*	.07
Contrast 1						.731	
Contrast 2						.018*	
Contrast 3						.441	
Arousals REM	11.34 (4.30)	13.50 (7.68)	12.46 (6.61)		0.949	.622	.00
LOS Total	61.69 (19.74)	65.73 (20.17)	60.33 (25.29)		0.94	.624	.00
LOS N1	20.79 (10.56)	19.95 (8.45)	20.38 (8.16)		0.000	.999	.00
LOS N2	27.86 (11.03)	30.86 (13.30)	27.46 (14.38)		1.168	.557	.00
LOS SWS	4.41 (2.68)	4.91 (2.94)	4.08 (2.83)		1.151	.562	.00
LOS REM	8.59 (4.78)	9.91 (3.74)	8.71 (6.60)		1.922	.382	.00

Note. Means are presented with standard deviations in parentheses. PSQI Global = Pittsburgh Sleep Quality Index global score; SQ = Sleep Quality; SE = Sleep efficiency; TST = Total sleep time; TIB = Time in bed; SOL = Sleep onset latency; WASO = Wake after sleep onset; N1 = Sleep stage one; N2 = Sleep stage two; SWS = Slow-wave sleep; REM = Rapid eye-movement sleep; LOS = Lightening of sleep. Contrast 1: CONTROL vs HE; Contrast 2: FAS vs CONTROL; Contrast 3: FAS vs HE. $^{*}p < .05$.

Regarding the fast spindles, they occurred on average for 780 milliseconds at a peak frequency of 13.34Hz and arose 6.94 times per minute. The sigma power for the sample associated with these spindles was 20.15 $\mu V^2/Hz$ corresponding to the amplitude of 21.71 μV. On average 11.95% of the fast spindles coupled with an SO. Peak coupling strength, the consistency with which the spindles coupled at the same point in the SO, was $M_{sample} = .19$ and they tended to couple at the phase of the SO wave corresponding to -1.03 radians (-59.01°) which equates to the a bit before the start of the SO-upstate which is very similar to results reported by Cox et al. (2018).

Table 3

Descriptive Characteristics and Between-Group Comparisons of SWS Microarchitecture, Childhood Hippocampal Volume and Memory Retention (N = 76)

	Group					
	CONTROL	HE	FAS/PFAS			
Variable	(*n* = 29)	(*n* = 23)	(*n* = 24)	F/X^2	*p*	Eta^2
SO Band	2.21 (1.04)	2.22 (0.80)	1.91 (0.93)	2.748	.253	.01
Delta Band	2.49 (0.66)	2.37 (0.55)	2.32 (0.62)	0.539	.586	.01
SWA Band	2.44 (0.67)	2.34 (0.54)	2.25 (0.65)	0.612	.545	.02
Fast Spindle						
Density	6.87 (1.94)	6.84 (2.00)	7.12 (1.98)	0.148	.863	.00
Amplitude	22.83 (5.99)	20.41 (3.65)	21.55 (5.66)	2.597	.272	.00
Duration	0.76 (0.06)	0.77 (0.06)	0.79 (0.07)	1.593	.210	.04
Frequency	13.35 (0.57)	13.36 (0.62)	13.33 (0.52)	0.217	.897	.00
Sigma Power	22.28 (14.03)	16.94 (6.55)	20.51 (12.04)	1.831	.400	.00
CP %	13.19 (7.95)	10.95 (6.63)	11.37 (6.09)	0.942	.624	.00
CP Strength	0.17 (0.10)	0.23 (0.19)	0.18 (0.12)	1.417	.492	.00
CP Phase	-1.34 (1.24)	-0.65 (1.44)	-0.99 (0.98)	4.309	.116	.03
Left HV	3.81 (0.34)	3.78 (0.31)	3.54 (0.26)	5.50	.006**	.14
Contrast 1					.933	
Contrast 2					.008**	
Contrast 3					.029*	
Right HV	3.64 (0.61)	3.72 (0.31)	3.41 (0.25)	12.427	.002**	.14
Contrast 1					1.00	
Contrast 2					.006**	
Contrast 3					.007**	
Story Retention	87.26 (24.26)	70.56 (27.60)	68.09 (24.84)	4.509	.014*	.11

Contrast 1					.055	
Contrast 2					.021*	
Contrast 3					.941	
List Retention	73.18 (24.32)	72.55 (12.19)	75.88 (18.58)	0.199	.82	.00

Note. Means are presented with standard deviations in parentheses. SO = Slow oscillation; SWA = Slow-wave activity; CP = Coupling; HV = Hippocampal volume in cm^3. Contrast 1: CONTROL vs HE; Contrast 2: FAS vs CONTROL; Contrast 3: FAS vs HE. $^{*}p < .05$. $^{**}p < .01$.

Hippocampal Volume and Memory Retention

When assessing childhood hippocampal volume for the sample (recorded at age 9-11), the left hippocampus was slightly larger with a mean of 3.72cm^3 than the right with a mean of 3.59cm^3 (difference approximately 0.10 cm^3; Biffen et al., 2020). With regards to memory retention, reflective of sleep-dependent consolidation processes, the sample retained 76.15% of story task information and 73.84% of the word list after the sleep-filled interval.

Testing Hypothesis 1

Identifying Potential Confounding Variables

A number of demographic variables and psychiatric symptoms/profiles were evaluated for between-group differences associated with FASD diagnostic category and for associations with continuous alcohol exposure in utero (AA/dd). These demographic and psychiatric variables were also evaluated for their relationship with the primary outcome (memory retention). These sets of analyse served to identify variables that could confound the primary analyses and would be added to subsequent models. The results showed several significant between-group differences or associations, with non-significant findings reported in Supplementary Table 1 (Appendix M).

Regarding age, although there were no observed between-group differences, spearman correlations revealed that AA/dd had a small negative association with participant age indicating

that as exposure increased so age decreased, thus, the younger participants have higher rates of dose-related alcohol exposure.

Sex did not have any between- or within-group differences across PAE. However, sex differences very close to accepted significance levels were revealed with regards to story retention (t (74) = 1.974, p = .052) and list retention (t (74) = 1.827, p = .071). In both instances individuals identifying as female retained more information after overnight sleep than males.

Furthermore, the analysis of SES as a covariate highlighted that the FAS/PFAS group had a significantly lower SES than the control and HE groups, with individuals in these latter two groups coming from similar SES backgrounds. This finding highlights that individuals with FAS/PFAS have lower levels of education and/or occupation. Spearman correlations also revealed that lower AA/dd was associated with higher SES scores and higher SES was also associated with better retention for the story task.

Anxiety scores, as measured by the BAI, did not differ between-groups, however a small negative association with word-list retention was observed, indicating that lower anxiety scores were associated with better word-list retention.

ICV, which was also uniform across groups, demonstrated small negative correlations with memory retention, indicating that smaller volume was associated with better story and list learning retention.

Both the nighttime and morning measurements of alertness, as measured by the SSS, were trending near defined significance levels for FASD group diagnosis. For nighttime alertness individuals with an FAS/PFAS diagnosis reported higher levels than controls and for morning they reported higher than HE individuals. Additionally, of the two alertness measurements, only the nighttime one had a small positive association with AA/dd indicating that higher alertness at

nighttime, before declarative information was presented for encoding, was associated with higher continuous PAE.

Cigarette use was the only substance that had potential to be a confounding variable, though this was not related to between-group differences. A pattern of higher use was associated with lower story retention.

Lastly, pre-laboratory sleep quality rating varied across groups with FAS/PFAS individuals rating their sleep quality as worse than healthy controls, though it still fell within the "OKAY" rating category (see Table 2). This finding was reflected in a small negative correlation indicating that higher dose-related in utero alcohol exposure was associated with worse prior sleep quality.

In summary, age, sex, SES, anxiety scores, ICV, nighttime alertness, cigarette use, and pre-laboratory sleep quality are potential confounds that may influence the associations between PAE and memory retention.

Hypothesis 1a: Objective SWS Characteristics.

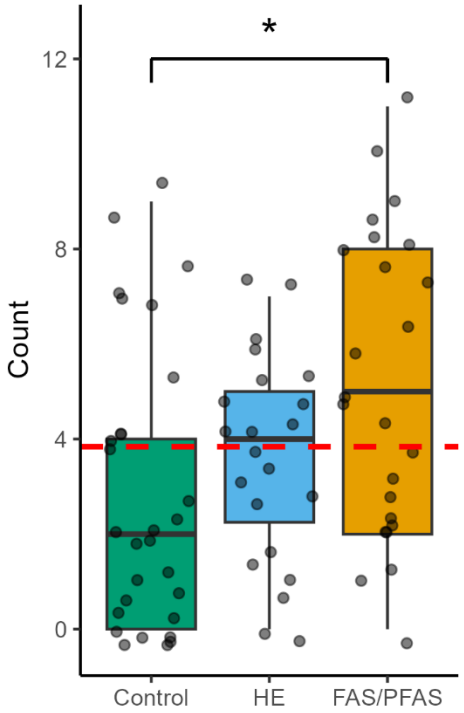
Tables 2 and 3 present the results showing between-group differences in objective SWS characteristics. I performed One-way ANOVAs and Kruskal-Wallis analyses depending on the normality characteristics of each variable. In terms of SWS macro-architecture, One-way ANOVAs revealed that participants did not differ in time spent in or percentage of SWS. Additionally, parametric and non-parametric analyses of SWS micro-architecture did not reveal differences in any of the PSD bands or fast spindle coupling parameters. However, while no significant between-group differences were observed for SWS arousals with LOS (those resulting in sleep stage-shifts to N1 or wake), they were revealed for SWS arousals without LOS (those disrupting SWS but not resulting in a stage-shift; Figure 1). Due to the skew nature of the

variable, which severely violated the normality assumption of ANOVA, I used a Kruskal-Wallis Rank Sum test. Post-hoc Dunn comparisons with Bonferroni correction revealed that individuals in the FAS/PFAS group had significantly more fragmented SWS with almost double the arousals without LOS than non-exposed individuals experienced during this deep sleep stage, highlighting disrupted SWS continuity for FAS/PFAS individuals.

I then examined AA/dd as a measure of continuous PAE in relation to SWS characteristics to determine if the results would reflect those found in the between-group analysis (Table 4). Spearman correlations were used due to the skew nature of the dose-related variable, given that most mothers report zero to very few drinks across pregnancy, with a smaller

Figure 1.

Boxplot of the Between-Group Differences in SWS Arousals



Note. The dashed red line is the grand mean. Significant between-group differences are noted. *p < .05.

percentage reporting a higher amount. In congruence with the between-group analysis no associations were revealed between AA/dd and SWS macro-architecture, arousals with LOS, PSD bands or fast spindle coupling percentage and strength. Additionally, a trend-level association was observed between AA/dd and SWS arousals without LOS whereby increased dose-related alcohol exposure leads to more fragmented SWS. There was no trend-level significance after adjustment for multiple comparisons. Unlike diagnostic group, AA/dd showed a small positive correlation with fast spindle coupling phase, meaning that higher alcohol consumption on each drinking occasion was associated with a more positive fast spindle coupling phase which corresponds to the up-state of the SO. However, after adjustment for multiple correlations, this association was not significant.

The between-group analyses demonstrate that PAE is related to SWS quality rather than quantity, highlighting that individuals with FAS/PFAS have more frequent arousals without LOS during SWS than healthy control participants. Continuous measures of PAE mirror these results with regards to fast spindle coupling phase but less convincingly, since the analyses did not remain significant after statistical correction. In summation, the results show that PAE is related to SWS micro-architecture and not macro-architecture, partially confirming the first hypothesis.

Hypothesis 1b: Hippocampal Volume

In order to determine whether those with FAS/PFAS have significantly smaller hippocampal volumes relative to HE and control individuals I performed both a One-way ANOVA and Kruskal-Wallis analysis (Table 3). A one-way ANOVA was used to assess differences in left-hippocampal volume due to its mild deviations in normality. Outliers in the data were winsorised (Abuzaid & Alkronz, 2024). Post-hoc Tukey HSD comparisons with Bonferroni correction revealed that the FAS/PFAS group had significantly smaller left

hippocampal volumes compared to the HE and control groups (Figure 2). When controlling for ICV (F (1, 67) = 2.580, p = .112) and sex (F (1, 67) = 0.152, p = .697) in an ANCOVA, neither variable changed the predictive value of PAE on left hippocampal volume (F (2, 67) = 5.555, p = .005) which remained significant. To assess for significant differences in right hippocampal volume, a Kruskal-Wallis Rank sum test was employed due to the severely skew nature of the variable. Right hippocampal volume demonstrated a similar pattern to the left hippocampal data.

Figure 2.

Boxplot of the Between-Group Differences in Left Hippocampal Volume

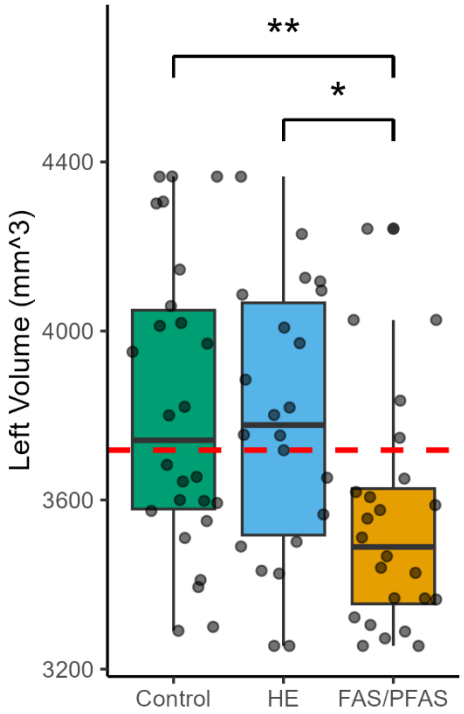
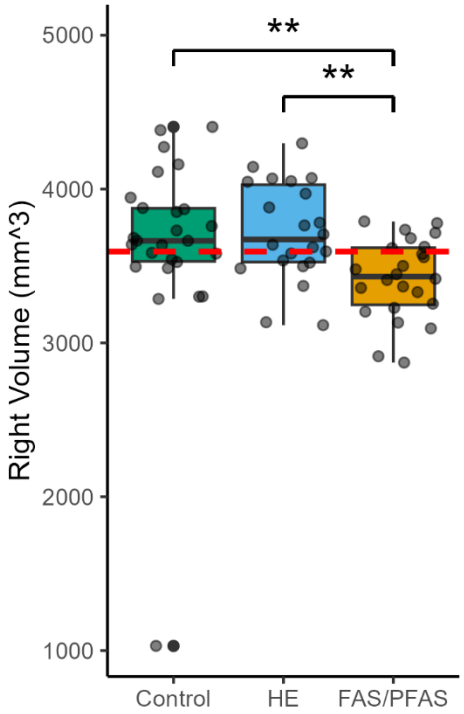


Figure 3.

Boxplot of the Between-Group Differences in Right Hippocampal Volume



Note. The dashed red line is the grand mean. Significant between-group differences are noted. *p < .05. **p < .01

Post-hoc Dunn comparisons with Bonferroni correction revealed that individuals in the FAS/PFAS group had significantly smaller volumes in the right-side region compared to controls

and HE individuals (Figure 3). An ANCOVA was not performed for right hippocampal volume due to its non-parametric nature.

Similarly to the between-group findings, AA/dd demonstrated a small negative correlation with left hippocampal volume signifying that higher doses of alcohol per drinking occasion were associated with smaller volumes in this region (Table 4). However, there was no significant association after adjustment. Additionally, no association between AA/dd and right hippocampal volume was observed.

Evidently, exposure to higher amounts of alcohol in utero, as evidenced through a FASD diagnosis, negatively impacts hippocampal development in late childhood compared to no or milder alcohol exposure. This was mirrored in the association between left (but not right) hippocampal volume and AA/dd, though once again less convincingly since the analysis was not significant after correction. In summation, congruent with the hypothesis, hippocampal volume was significantly smaller for those with an FAS/PFAS diagnosis compared to individuals with lower exposure, for both left and right sides.

Hypothesis 1c: Between-Group Differences in Memory Retention

Memory retention was separated into the two task categories, story and list learning retention. Both variables had only mild deviations in normality and therefore were assessed using One-way ANOVAs. Though memory retention did not differ between-groups for list learning retention (Figure 5), differences were observed in story retention (Figure 4). Post-hoc Tukey HSD tests with Bonferroni correction showed that individuals in the FAS/PFAS group retained significantly less information relating to the story task than healthy controls after a sleep-filled delay. Interestingly, HE individuals' performance showed trend-level significance indicating a similar pattern of difference in retention as the FAS/PFAS and control comparison. This indicates

that the effects of PAE on memory retention are strongest when FASD status is diagnostically relevant, but that there are also some mild effects with exposure that does not result in a diagnostic phenotype.

Furthermore, I statistically controlled for SES, cigarette use and sex due to the significant between-group differences in SES and the relationship of the variables to story retention. An

Figure 4.

Boxplot of the Between-Group Differences in Story Retention

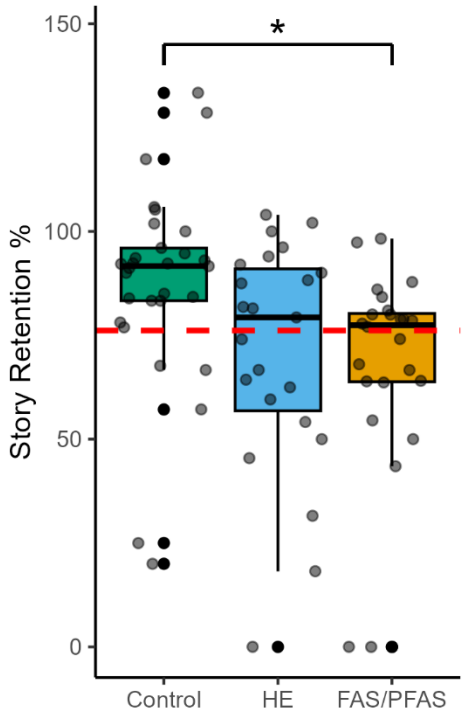
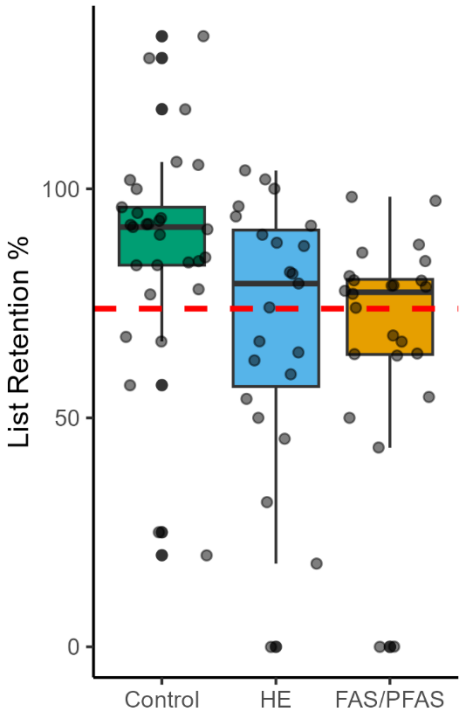


Figure 5.

Boxplot of the Between-Group Differences in List Retention



Note. The dashed red line is the grand mean. Significant between-group differences are noted. *p < .05.

ANCOVA revealed that FASD diagnosis remained significant (F (2, 70) = 5.014, p = .009) alongside SES (F (1, 70) = 6.467, p = .013) as a predictor of memory retention. Cigarette use and

sex, however, were not significant predictors of story retention (F (1, 70) = 0.076, p = .783; F (1, 70) = 1.185, p = .280). These findings demonstrate that individuals with FAS/PFAS in comparison to healthy controls have poorer memory retention, even after correcting for SES, cigarette use and sex, pointing to a disruption in overnight consolidation in this group.

The analysis of continuous PAE echoed these results (Table 4). The strongest association found in the correlation analysis was between dose-related PAE and story retention. A moderate negative relationship between the two variables highlighted that alcohol consumption during pregnancy is associated with poorer story retention and thus, consolidation of the task. This finding remained significant after adjustment for multiple correlations demonstrating the strong relationship between dose-related PAE and poorer memory retention for the more contextual task. This is in comparison to the spindle and hippocampal associations which did not survive adjustment indicating potentially less meaningful associations with AA/dd. These analyses are consistent with the hypothesis that those with more severe PAE show worse memory retention when compared to individuals with mild or no exposure.

Summary of Hypotheses A-C

Regarding SWS, the strongest findings showed diagnostic differences regarding SWS arousals without LOS while the continuous measure did not fully reflect these between-group findings. Additionally, hippocampal volume was strongly related to PAE with regards to FASD status, however less convincingly or not at all for AA/dd. Nevertheless, story retention was most notably related to PAE whether analysed using a diagnostic or dose-related approach. Unexpectedly, dose-related PAE did not fully reflect the results demonstrated in between-group analyses. This highlights that diagnostic classification and continuous measures of PAE may be

Table 4

Correlations Between Dose-related PAE and SWS Characteristics, Childhood Hippocampal Volume and Memory Retention (N = 76)

Variable	*r*	*p*	*p-adjusted*
AA/dd x SWS min	-.06	.588	.686
AA/dd x SWS %	-.06	.574	.686
AA/dd x SWS Arousals	.21	.059	.207
AA/dd x SWS Arousals LOS	.07	.541	.686
AA/dd x SO PSD	.00	.991	.991
AA/dd x Delta PSD	-.07	.521	.686
AA/dd x SWA PSD	-.06	.578	.686
AA/dd x Fast Coupling %	-.14	.226	.528
AA/dd x Fast Coupling Phase	.27	.019*	.133
AA/dd x Fast Coupling Strength	.07	.543	.686
AA/dd x Left HV	-.25	.034*	.163
AA/dd x Right HV	-.19	.096	.269
AA/dd x Story Retention	-.47	< .001***	< .001***
AA/dd x List Retention	.04	.691	.744

Note. Means are presented with standard deviations in parentheses. AA/dd = Absolute alcohol consumed per drinking day; SWS = Slow-wave sleep; LOS = Lightening of Sleep; SO = Slow Oscillation; PSD = Power Spectral Density; SWA = Slow-wave Activity; HV = Hippocampal Volume. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

sensitive to picking up unique relationships related to SWS and hippocampal volume as they measure hypotheses that those with slightly different phenomena relating to PAE. Nevertheless, the analyses support the more severe PAE experience poorer SWS quality, have smaller hippocampal volumes and worse memory retention, in comparison to individuals with lower PAE.

Hypothesis 2a-b: Exploring the relationship between PAE, hippocampal volume, SWS characteristics and memory retention

Examining the Correlations with SWS

Based on correlations between SWS variables and memory retention scores that were performed to limit the number of SWS variables used in the model building process, a number of associations emerged (Supplementary Table 2; Appendix N). SWS macro-architecture (SWS minutes and percentage) was not associated with story retention, however, elements relating to the micro-architecture of SWS were significant, specifically fast spindle properties. Moderate negative correlations were found between story retention and both fast spindle duration (r = -.34; p = .002) and fast coupling phase (r = -.30; p = .007). These demonstrate that longer fast spindle durations and more positive fast spindle coupling phases are associated with poorer neutral declarative memory retention over a sleep-filled delay. A small negative association was found for fast coupling strength (r = -.24; p = .031) demonstrating that as coupling strength increases so story retention gets worse. Lastly, a small positive correlation was also found for fast spindle coupling percentage (r = .24; p = .034). This indicated that an increased coupling rate in fast spindles was associated with better neutral declarative memory retention in the story memory task. Taken together, these results indicate that shorter spindle durations, with less positive coupling phase and lower strength (that is, the similarity of coupling events during the SO), but occurring at a more frequent rate, are spindle properties associated with better story retention.

In comparison to story retention, list retention was associated more consistently with the macro-architecture of sleep. Both SWS minutes (r = .24; p = .032) and percentage (r = .23; p = .039) showed small positive associations with list retention indicating longer periods of SWS were associated with improved word-list retention. With regards to the micro-architecture of

SWS, improved list retention performance was associated weakly with fewer SWS arousals with LOS (r = -.23; p = .038).

Regression analysis: Story Retention

Using the information gleaned from the correlation analysis, I formulated the linear models to predict the retention of story-related information after a period of sleep using measures of PAE, hippocampal volume, the objective SWS moderators (fast spindle duration and fast spindle coupling phase, strength and percentage) and previously identified potential covariates (age, sex, SES, nighttime alertness (SSS), cigarettes per day, ICV and pre-laboratory average sleep quality). Interactions between SWS, PAE and hippocampal volume were also generated with the goal of determining whether they influence each other's relationship to memory retention.

The model-building process revealed that of the two kinds of measures of PAE, the best models all included the continuous measure of AA/dd rather than diagnostic group. Therefore, the models including FASD diagnosis as a representation of PAE have been included in the appendix as Supplementary Table 3 (Appendix O) even though their results were largely similar to those of the AA/dd models, but weaker in strength.

The model examining fast spindle duration also included AA/dd, SES and ICV as predictors and accounted for 26.06% of the variance in story retention scores over a sleep-filled delay (see Table 5). Regarding the main effects of AA/dd, which was a significant predictor of story retention before the addition of covariates, higher doses no longer predicted poorer retention after controlling for ICV. Nevertheless, the moderate effect size demonstrated that it contributed variance to the overall model. In comparison to AA/dd, fast spindle duration maintained a significant main effect demonstrating that longer spindle durations predict worse

Table 5

Linear Regression Models: Predicting Retention of Neutral Declarative Information, through a Story Task, over a Sleep-filled Delay using Dose-related PAE, Childhood Hippocampal Volume, SWS Micro-architecture and Covariates (N = 76)

	Estimate	*SE*	*p*	*Eta*^{2}
Variable				
Intercept[a]	194.00	42.90	< .001***	
AA/dd	-2.10	1.24	.094	.10
Fast Spindle Duration	-108.70	42.30	.012*	.15
SES	0.87	0.39	.030*	.08
ICV	-3.781e-05	1.928e-05	.054	.06
Intercept[b]	226.40	62.70	< .001***	
AA/dd	-3.38	1.24	.008**	.15
Fast CP Strength	-644.00	268.70	.019*	.11
Left HV	-0.03	0.01	.038*	.00
SSS $_{\text{Nighttime}}$	3.77	2.23	.096	.09
SES	1.06	0.38	.007**	.12
ICV	-4.715e-05	1.885e-05	.014*	.07
Fast CP Strength x Left HV	0.16	0.07	.034*	.07
Intercept[c]	63.08	12.04	< .001***	
AA/dd	-3.02	1.23	.016*	.13
Fast CP %	0.87	0.39	.029*	.08
SES	0.72	0.38	.065	.08
Sex Male vs Female	-13.46	5.57	.018*	.08

Note. AA/dd = Absolute alcohol consumed per drinking day; SES = Socio-economic status; ICV = Intracranial volume; CP = Coupling; HV = Hippocampal Volume; SSS = Stanford sleepiness scale. [a]Fast Spindle Duration:

Adjusted R^2 = 26.06%, F (4, 66) = 7.168, p < .001; [b]Fast Spindle Coupling Strength: Adjusted R^2 = 34.82%, F (7, 63) = 6.343, p < .001; [c]Fast Spindle Coupling Percentage: Adjusted R^2 = 24.72%, F (4, 70) = 7.076, p < .001. *p < .05. **p < .01. ***p < .001.

retention outcomes for the story task.

No interactions were observed during the model-building process, illustrating that there was no interplay between the central variables as well as no moderating effect of fast spindle duration on either PAE or hippocampal volume in relation to the consolidation of story-related information. When assessing the covariates I decided to retain ICV within the model despite it dampening the significance of AA/dd because ICV improved model fit, had a substantial beta-coefficient, was trending closely towards accepted significance levels and had a moderate effect size. Reflective of the correlation analysis, larger ICVs predicted worse retention scores. Lastly, SES was a significant covariate and showed that higher SES predicted better story retention with the moderate effect size pointing to its important role in explaining the consolidation of story-related information.

The model building process revealed that fast spindle coupling strength, alongside the other covariates, explained the largest amount of variance in story retention scores accounting for 34.82% of the variance. The model also included the covariates AA/dd, left hippocampal volume, nighttime alertness, SES, ICV and the interaction of fast spindle coupling strength and left hippocampal volume. AA/dd has the strongest main effect, showing that higher doses of alcohol per drinking occasion predict poorer retention. The estimate of fast spindle coupling strength was also significant with a slightly smaller though still moderate effect size. It predicted that increases in coupling strength worsened retention scores, congruent with the negative association in the correlation analysis. This implies that increases in the consistency with which fast spindles couple at the same time is worse for story retention. A negative estimate was also

observed for left hippocampal volume indicating that larger volumes are associated with poorer retention. However, the significance of its main effect should be interpreted with caution given the negligible effect size ($\eta^2 = .005$) and unexpected direction.

Although no three-way interaction was revealed, an interaction effect was observed between fast spindle coupling strength and left hippocampal volume. To examine the interaction, I assessed the slopes between coupling strength and story retention across left hippocampal volume groupings. I chose to visualise the relationship this way because the relationship between story retention and hippocampal volume is weak compared to coupling strength. Thus, plotting volume against retention and assessing for altered relationships across high and low coupling strengths would not be successful due to overall weak relationship regardless of other factors. Since I know that the interaction is significant and moderate in terms of effect size, I chose to assess it from a different angle, grouping hippocampal volume into low and high-volume categories (see Figure 6). The larger volume group had a non-significant slope ($p = .915$) demonstrative of the lack of relationship between story retention and fast spindle strength. However, the smaller volume group had an inverse and significant slope ($p < .001$) which was significantly different from the larger volume group's slope ($p = .025$). For the smaller volume group, this indicated that fast spindle strength does impact story retention performance. Specifically, for this group it is more beneficial for consolidation if fast spindles couple less regularly. In contrast, consolidation for those with larger volumes is not impacted by coupling strength.

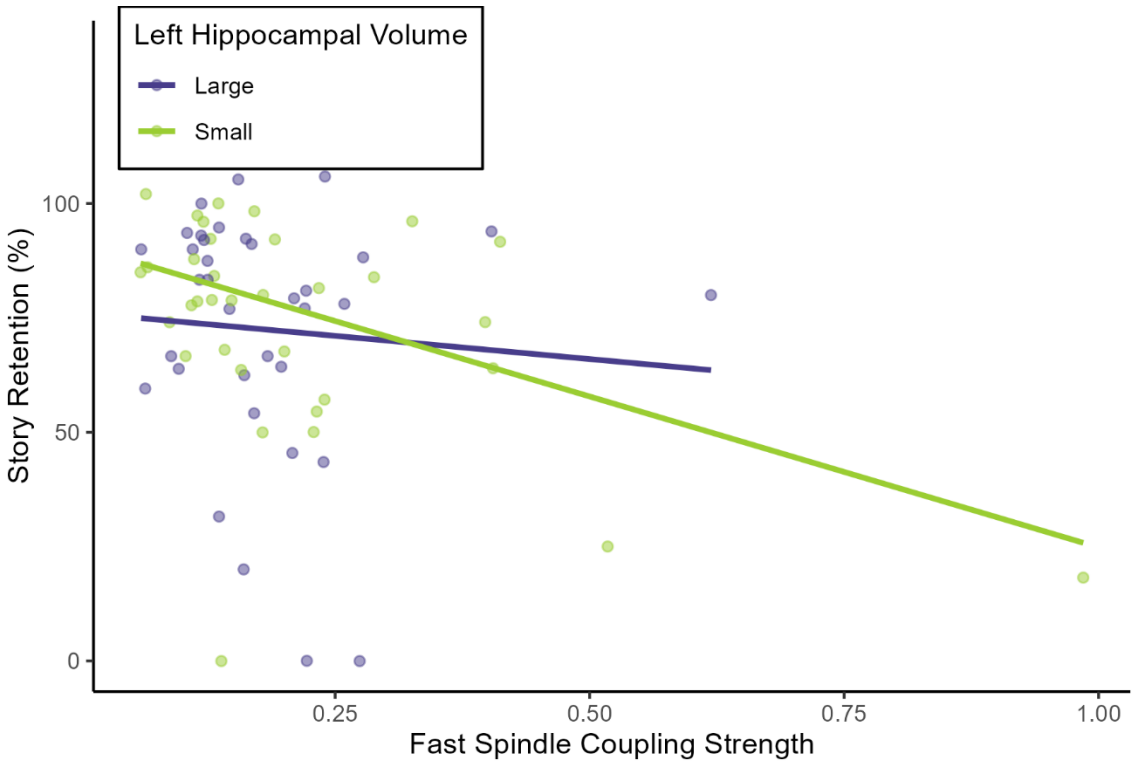
As a covariate the nighttime alertness estimate showed that increases in subjective alertness during encoding predicted improved overnight retention for complex neutral declarative memory. I kept alertness as a covariate, despite it not reaching significance as a predictor, due to

its moderate effect size. As in the previous model higher SES predicted better story retention while larger ICVs predicted worse scores and both effect sizes point to their important role in explaining the consolidation of story memory.

The final model to predict the retention of story-related information included AA/dd, fast spindle coupling percentage, SES and sex and accounted for 24.72% of the variance in retention outcomes. AA/dd had a significant main effect and followed the same predictive pattern as the previous models. Similarly, fast spindle coupling percentage had a significant main effect, with a moderate effect size, showing that increases in the percentage of fast spindles coupling with SOs predicted better story retention. Once again, no interactions were observed during the model-

Figure 6.

Scatter Plot Showing the Interaction Between Fast Spindle Coupling Strength and Left Hippocampal Volume



Note. Left hippocampal volume split into two groupings using the median.

building process, demonstrating an absence of a three-way interaction as well as indicating that fast spindle coupling percentage does not have a moderating effect on the relationship between PAE/hippocampal volume and consolidation for story retention. Regarding the covariates, I decided not to include ICV as its effect size was small (η^2 = .05; .04) and it was only trend-level as a predictor. Once again SES maintained a moderate effect size compared to the other predictors, though unlike the other models it was only trend-level with moderate effect. Sex was a significant predictor with a moderate effect size. The estimate indicated that those identifying as male had worse retention scores than those identifying as female.

Comparing the spindle parameters assessed in each model, fast spindle duration had the largest effect size, explaining the highest amount of variance in the story retention outcome, followed by fast spindle coupling strength and lastly, coupling percentage. Nevertheless, all effect sizes were moderate to large highlighting the contribution of SWS micro-architecture to consolidation of the story task. Overall, the fast spindle coupling strength model was the best when considering variance explained, model complexity and the effect sizes associated with all predictors.

The other models that were assessed can be found in Supplementary Table 2 (Appendix O). Predictors and covariates that were not significant within any model included fast spindle coupling phase, right hippocampal volume, age, current cigarette use and average sleep quality.

Regression analysis: List retention

The model-building process followed the same method as that was used for the story retention models. The SWS moderators included SWS minutes, SWS percentage, SWS arousals with LOS. Relevant demographic and clinical variables included age, sex, SES, BAI, nighttime

alertness (SSS), ICV and pre-laboratory average sleep quality. The model-building process revealed that only FASD group was a significant predictor within the list retention models, rather than AA/dd which was the most effective of the two PAE predictors in the story retention models.

The model including SWS percentage was the most successful in terms of explaining the variance in the list retention outcome. SWS minutes also generated a very similar model, due to both SWS characteristics being measures of SWS quantity. However, it has been included in Supplementary Table 4 (Appendix P). The best model including SWS percentage, FASD group, a SWS percentage x FASD group interaction and covariates including average sleep quality and BAI score (Table 6). It accounted for 21.70% of the variance in list retention outcomes. Regarding the main effects, FASD group had significant main effects only for the HE vs healthy control comparison and not the FAS/PFAS vs healthy control comparison. Thus, in comparison to the dummy variable, the control group, individuals with heavy exposure but not an FAS/PFAS diagnosis predicted poorer word-list retention. However, the FASD diagnostic group had a very small effect size demonstrating little contribution to word list retention. In contrast, SWS percentage had a moderate significant main effect size that showed that an increase percentage of time spent in SWS was beneficial for the retention of a word list.

Although no three-way interaction was observed, a two-way interaction effect was revealed between SWS percentage and FASD group, which indicated that SWS macro-architecture moderates the relationship between PAE measured diagnostically and word-list retention. In comparison to the FASD group predictor, the interaction had a moderate effect size emphasising its contribution to the model. Specifically, the significant interaction was between SWS percentage and individuals in the HE group in comparison to healthy controls. I further

examined the interaction visually (Figure 7) and via slope analysis. The analysis indicated that the impact of SWS macro-architecture on list learning retention changed across the FASD

Table 6

Linear Regression Models: Predicting Retention of Neutral Declarative Information, through a Word-list task, over a Sleep-filled Delay using FASD Diagnostic Group, SWS Macro-architecture and Covariates (N = 76)

	Estimate	*SE*	*p*	*ESE*
Intercept	79.18	15.59	<.001***	
FASD Group				.00
FASD HE vs HC	29.78	13.56	.031*	.21
FASD FAS vs HC	11.72	13.60	.391	.15
SWS %	1.65	0.56	.004**	.10
Ave SQ Pre	-6.91	2.89	.019*	.05
BAI	-0.58	0.19	.003**	.13
SWS % x FASD Group				.09
SWS % x HE vs HC	-2.08	0.80	.012*	.12
SWS % x FAS/PFAS vs HC	-0.89	0.76	.249	.05

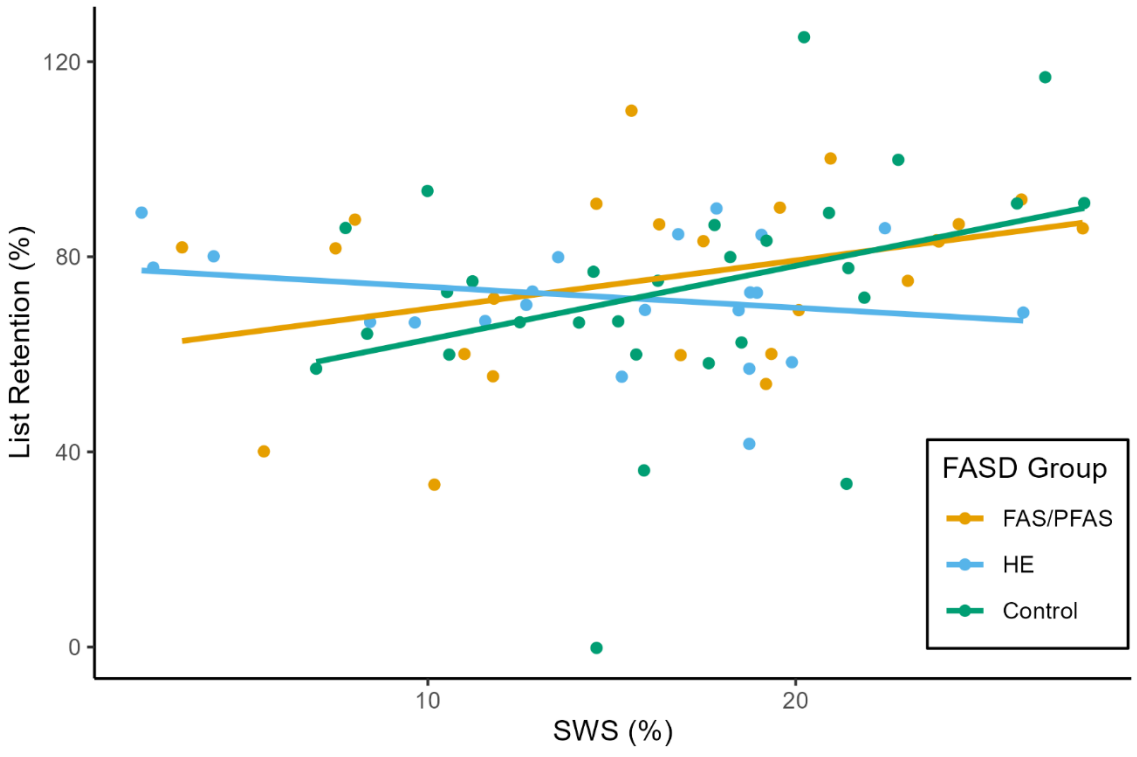
Note. SWS = Slow-wave sleep; HE = Heavily exposed; HC = Healthy controls; FAS/PFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; SQ = Sleep quality; BAI = Beck anxiety inventory. SWS % x FASD Group = Interaction term between SWS percentage and diagnostic group, not included in model but to assess its contribution to variance. SWS % x HE vs HC = Interaction effect between SWS percentage and diagnostic group comparing HE to healthy control individuals. SWS % x FAS/PFAS vs HC = Interaction effect between SWS percentage and diagnostic group comparing FAS/PFAS to healthy control individuals. SWS percentage: Adjusted R^2 = 21.70%, F (7, 66) = 3.890, p = .001. ESE = Effect size estimate: Eta^2 all variables except for individual FASD group contrasts for which standardised mean difference was calculated and individual FASD group interactions for which residual standard deviation was used. *p < .05. **p < .01. ***p < .001.

diagnostic groups. Healthy control individuals demonstrated a significant, steep positive slope (p = .004) indicating that individuals' word-list performance in this group was more greatly

influenced by increases in SWS. However, the positive slope for individuals in the FAS/PFAS was not significant (p = .142), which was the same for HE individuals who had a slightly negative slope (p = .463). Therefore, the retention of word-list material was not strongly tied to increases in SWS for individuals in the FAS/PFAS and HE groups. The only significant difference was between the control and HE slope (p = .032) as highlighted in Figure 4 with the strong positive relationship for the control individuals and slightly negative relationship for HE individuals. Thus, the percentage of time spent in SWS had a greater positive effect on list retention for healthy controls than for HE individuals which had almost no relationship. Furthermore, participants in the HE group had a lot less variation in the relationship between SWS percentage and list retention, compared to the other groups which have a wider spread of

Figure 7.

Scatter Plot Showing the Interaction Between SWS Percentage and FASD Diagnostic Categories



the data. Nevertheless, both alcohol-exposed groups had slopes that were not significant. Overall, this provides evidence that time spent in SWS impacts consolidation positively when individuals have low PAE from a diagnostic standpoint, while increases in SWS percentage do not confer a retention advantage for those with PAE.

With respect to the covariates, poorer average sleep quality in the week prior to the study predicted better word-list performance, though this had a small effect size, while lower anxiety scores predicted improved word-list retention, which showed a moderate effect size.

In contrast to the story retention models, hippocampal volume was not a significant predictor of list retention. The model assessing arousals with LOS during SWS is in Supplementary Table 4 (Appendix P) and was not included due to its poor explanation of variance. Overall, arousals with LOS, hippocampal volume, age, sex, SES, nighttime alertness and pre-laboratory average sleep quality were not significant predictors in any of the models.

Summary of the Regression Analyses

These models indicate that the neutral declarative memory task that requires memory for information that is contextually connected (i.e. recalling details of a story) is associated with the finer micro-architecture specific to SWS and reflective of its quality, specifically with the properties of fast spindles generated during SWS. This is distinct from list retention which is associated with broad aspects of SWS macro-architecture. Thus, both SWS micro- and macro-architecture are salient for consolidation processes as predicted. However, contrary to the hypothesis the results do not support a three-way interaction between SWS, PAE and hippocampal volume for retention. Nevertheless, there is some evidence that SWS variables moderate retention performance either through a hippocampal pathway (story task) or regarding FASD diagnostic group (word list task).

Discussion

This study set out to investigate how PAE, measured both diagnostically (FASD diagnostic categories) and continuously (measures related to the number of units of alcohol consumed during pregnancy) may be related to objective SWS macro- and micro-architecture, childhood hippocampal volume and neutral declarative memory retention. Following this, I wanted to determine whether SWS micro- and/or macro-architecture were involved in consolidation of the declarative tasks as well as whether the relationship between in-utero alcohol-exposure, hippocampal volume and SWS was inter-related to influence memory consolidation. Specifically, I proposed that individuals with PAE who have smaller hippocampal volumes and altered SWS would have poorer consolidation for the two tasks. These aims are grounded in established models of memory that highlight the impact of PAE and the critical role of SWS and the hippocampus in memory consolidation.

Between-group Differences in, and PAE Associations with Central Variables

SWS-Architecture

Given the lack of objective sleep data recorded for those with PAE, my first aim was to characterise and compare their SWS architecture from objective polysomnographically recorded sleep. I examined both the macro- and micro-architecture of this sleep stage as it has not been described in individuals exposed prenatally to alcohol, especially in a young adult sample. This is despite known subjective and objective sleep difficulties stemming from childhood. I proposed that those with more PAE would have less time spent in SWS, more fragmented SWS, lower SWS-depth across the three PSD bands, and altered fast spindle properties. These hypotheses sought to show that in utero alcohol-exposure was related to disrupted SWS.

The analysis revealed that both the macro-architecture of SWS (minutes and percentage) as well as most aspects of the micro-architecture were unaffected by PAE. Thus, contrary to the hypotheses participants with and without PAE had similar amounts of (a) time spent in SWS, (b) arousals with LOS that led to sleep stage-shifts, (c) SWS-depth across each band and (d) fast spindle properties.

Nevertheless, a significant difference for one aspect of SWS-micro-architecture was observed. The findings showed that those diagnosed with FAS/PFAS had almost double the number of arousals during SWS in comparison to control participants. Specifically, these were arousals that did not result in a sleep stage-shift but rather a short disruption within the deep-sleep period. With regards to a prenatal alcohol dose-related relationship with SWS arousals, there was only a trend-level association that did not survive adjustment. Overall, the results demonstrate a very specific deficit in mechanisms of sleep maintenance, resulting in more SWS fragmentation that varies with FASD diagnosis, rather than alcohol dose-related exposure. There was an additional SWS-related variable, fast spindle coupling phase, that had a dose-related relationship; however, it was also not maintained when correcting for multiple comparisons. Specifically, maternal reports of PAE were associated with a more positive fast spindle coupling phase which corresponds to the up-state of the SO.

These findings suggest that the definition of PAE is important when examining its associations with SWS. FASD diagnostic categories seem to be more sensitive for capturing relationships with SWS variables compared to the dose-related approach. Speculatively, this may be because PAE that produces visible dysmorphic alterations is more likely to also impact the development of brain structures which are consequently involved in the generation of slow waves. S. Y. Chen and Kannan (2023) and Zhou et al. (2003) have illustrated how neural crest

cells, involved in cranio-facial development, and the neural tube (premature central nervous system) are damaged through ethanol exposure. Both structures evolve together very early during development, and thus, high doses of alcohol exposure during early developmental periods would likely affect both facial and brain formation. The dose-related approach, which reflects alcohol exposure along a continuum, may not capture the effects of alcohol exposure, because a measure of units of alcohol does not take into account the timing of exposure, which may influence dysmorphic features that are reflected in a diagnosis of FASD.

The SWS macro-architecture results were congruent with the few objective sleep studies examining polysomnographically recorded sleep in children with a FASD diagnosis. All three studies, which ranged from very small to medium sample sizes, found that FASD status was not associated with changes in SWS that differed from non-exposed controls (M. L. Chen et al., 2012; Dyląg et al., 2021). The current study reinforces these preliminary findings that perhaps PAE does not affect SWS quantity. It is interesting to note that these findings contrast with rodent studies that demonstrate PAE doses mimicking binge-drinking exposure result in shorter periods of and time spent in SWS (Apuzzo et al., 2020; Lewin et al., 2018; Volgin & Kubin, 2012; D. A. Wilson et al., 2016). Thus, the human studies provide evidence that these animal models may not fully represent the nuanced central nervous system changes that occur within humans, although more objective sleep data is needed to corroborate on the current findings in the literature.

Very few studies have examined power bands during sleep in individuals with FASD, with most assessing daytime awake EEG measures (e.g. Candelaria-Cook et al., 2021). The current study found that PSD did not differ in a significant manner between-groups and was not associated with maternal reports of binge-drinking exposure. These results align with those

reported by Kaneko et al. (1996) whereby delta band power was equal between individuals with a FASD diagnosis and non-exposed controls during overnight sleep. However, the current results differ when compared to what has been reported in sleep in infants with PAE. In a review of the literature Inkelis and Thomas (2018) described visually larger amplitudes and increases in power for alpha, beta, theta and delta bands during the equivalent of NREM and REM sleep compared to unexposed infants. Nevertheless, this change was observed only up to six weeks postnatally and may not reflect what occurs in the sleep of adults with PAE. Typically, non-exposed adults tend to have more attenuated SWA, which propagates from frontal regions, whereas pre-pubescent children have higher, more posteriorly located SWA (Ringli & Huber, 2011). Therefore, differences in PSD between exposed and non-exposed individuals may be more easily discerned with posterior electrode placement during the pre-pubescent stages of development. This is because differences in the generation of slow waves may be more noticeable and reflect differences in cortical maturation and development in individuals with PAE.

Unfortunately, as no studies have examined spindle architecture in those with PAE, it cannot be said whether the similarities found between alcohol exposed and non-exposed individuals align with what has previously been found. Compared to previous studies examining fast spindles in healthy individuals the current study's fast spindle results for the sample showed that they occurred at a similar frequency to Mölle et al. (2011) but higher than Guadagni et al. (2021). Their density was also similar to the number of central fast spindles reported during combined N2 and SWS (Denis et al., 2021a) and far greater than the fast spindle density reported in SWS for Guadagni et al. (2021). Lastly, their amplitude and sigma power (μV^2/Hz) were slightly lower than what was reported in the meta-analysis by Ng et al. (2024). Regarding coupling, fast spindles for the sample coupled with an SO only half as much as what was

reported in Ng et al. (2024) and Denis et al. (2021a). Peak coupling strength, the consistency with which the spindles coupled at the same point in the SO, was only slightly lower than results found for Cox et al. (2018), though much lower than reported by Ng et al. (2024). Fast spindles tended to couple at the phase of the SO wave corresponding to the start of the SO-upstate which is very similar to those reported by Cox et al. (2018) but a lower phase than Ng et al. (2024). Overall, the current sample, including exposed and non-exposed individuals, does largely reflect results from studies examining healthy individuals with some deviations with reference to density and coupling parameters. Although given the lack of between-group differences, these deviations are unrelated to in utero alcohol exposure and are reflective of the sample. The only aspect of the spindles that showed a fleeting association with maternal reports of PAE, before adjustment for multiple correlations, was fast spindle coupling phase.

The results concerning SWS fragmentation are the most consistent with the literature examining objective sleep in individuals diagnosed with FASD, though this has not been specific to SWS (M. L. Chen et al., 2012; Dyląg et al., 2021; Goril et al., 2016). It is important to note that the current sample had highly fragmented sleep irrespective of PAE when examining the arousal index, and arousals across all sleep stages. In fact, double the arousal index value of previous FASD studies were reported (M. L. Chen et al., 2012; Dyląg et al., 2021; Goril et al., 2016). This may be related to the sample experiencing more N1 sleep than what is normally observed as many participants live in low SES environments in South Africa which are characterised by a lack of secure housing and high levels of nighttime noise and violence (Correia et al., 2024). These circumstances fuel fear regarding one's safety during sleep which has been associated with poorer subjective sleep ratings, particularly for men (Correia et al., 2024). In addition, Lipinska and Thomas (2017) reported that in a sample of participants from

low SES areas, many preferred the quiet of the sleep laboratory environment as well as its perceived level of safety as opposed to home environment disruptions stemming from other household members, traffic and gun shots. This sample also had highly fragmented sleep. Furthermore, these sleep fears have also been associated with dysregulated nervous system activation (Mellman et al., 2018), perhaps contributing to a more hypervigilant sleep state where one is primed for alertness resulting in lighter and more fragmented sleep in the sample.

Despite this observation, the increased SWS arousals for individuals with FAS/PFAS point to a specific deficit in SWS maintenance that does echo the general sleep fragmentation findings reported in the prior literature as well as deep-sleep disruptions observed in rodent models (Apuzzo et al., 2020; Lewin et al., 2018; Volgin & Kubin, 2012; D. A. Wilson et al., 2016).

Our results present support for previous studies in humans showing that PAE does not impact SWS quantity as has been suggested by animal models. Additionally, it supports studies showing high rates of fragmentation across sleep, and that this is specifically reflected during SWS, the deepest sleep stage which typically has the fewest arousals. Lastly, SWS micro-architecture relating to depth and spindle parameters are also shown not to be altered as a result of PAE or meaningfully associated with PAE. These findings suggest that PAE plays a role in affecting SWS quality, specific to fragmentation, rather than quantity, which has been shown to be the more important factor in SWS consolidation mechanisms.

Hippocampal Volume

My second hypothesis was to determine whether higher in utero alcohol-exposure was related to reductions in childhood hippocampal volume. The results clearly supported this proposition. Individuals in the FAS/PFAS group had smaller left and right hippocampal volumes

on average than individuals in both the HE and control groups. This remained true even when controlling for individuals' ICV and sex highlighting that regardless of one's overall brain volume and identified sex, those with a FASD diagnosis had abnormally small hippocampi. It is important to account for ICV within analyses assessing specific brain regions. Neglecting to do so may cause one to attribute local brain region differences to specific disease processes when they are in fact due to confounding individual differences in one's overall brain volume or skull size (O'Brien et al., 2006). I used a more favoured adjustment approach to correct for ICV, adding it as a covariate in an ANCOVA (J. Wang et al., 2024). It is especially important to control for ICV within this cohort as PAE and a diagnosis of FASD are associated with growth abnormalities and microcephaly (Archibald et al., 2001; Coles et al., 2011; Riikonen et al., 2005; Willoughby et al., 2008). Thus, their hippocampal volumes may appear much smaller than individuals with mild or no exposure merely due to their smaller head sizes which result in a proportionally smaller hippocampus. Researchers can then make more adequate judgements about hippocampal volume in relation to cognitive functions.

The diagnostically-relevant differences were also partially supported by results from the maternal reports of PAE which showed that increased doses of alcohol per drinking occasion were also associated with smaller hippocampal volumes, although only for the left side. However, this association did not remain relevant when adjusting for multiple comparisons. Therefore, as in the SWS analysis, dose-related PAE is not as successful a marker of differences in regional hippocampal volume compared to FASD status. Evidently, alcohol-exposure during pregnancy resulting in a diagnosis of FAS/PFAS negatively impacts the development of the central nervous system, particularly the hippocampus, which persists into childhood.

The literature examining neuroanatomical alterations in individuals with PAE compared to those without exposure have also reported significantly smaller hippocampi when accounting for ICV (Coles et al., 2011; Nardelli et al., 2011; Willoughby et al., 2008) although some found that accounting for ICV negated significant findings (Gross et al., 2018; Riikonen et al., 2005). In support of the results, Nardelli et al. (2011) observed that both hippocampi were reduced in individuals with FASD compared to healthy controls. Other literature only partially aligned with the current results, observing differences in only a single side. In a small sample of adolescents, PAE was only associated with smaller left hippocampal volumes in comparison to unexposed individuals even when controlling for ICV which was not found for the right side (Willoughby et al., 2008). A larger study of young adults, separated into three exposure groups (non-exposed, ARND and dysmorphic), found the opposite pattern, with only right hippocampal volume being affected by increasing PAE related to diagnostic group (Coles et al., 2011). Combined hippocampal volume was also the most reduced for the dysmorphic group, which also resembles the current findings.

In contrast to the results, Riikonen et al. (2005) observed that individuals with a diagnosis of FAS and those with exposure but without a diagnosis only had smaller left and right hippocampal volumes when ICV was not accounted for. This was in comparison to children without PAE who had undergone magnetic resonance imaging (MRI) scans due to varying health concerns, but that had normal findings. Results from Gross et al. (2018) mirrored the former whereby individuals classified as having heavy PAE, derived from maternal reports, had smaller hippocampi compared to healthy controls. Nevertheless, this finding was also not retained when accounting for ICV as the correction for multiple comparisons resulted in a more stringent significance threshold.

Contradicting our findings, Archibald et al. (2001) observed in a medium sized sample of children and early adolescents, that hippocampal volume was preserved in individuals diagnosed with FAS. Additionally, some studies have shown that the way hippocampal volumes are measured may alter results: Solar et al. (2022) found reduced hippocampal volumes in individuals with PAE during manual imaging assessments, but automated processes did not reveal the same alterations between-groups. Only specific subregions, such as the hippocampal body and tail, differed between those classified as being prenatally exposed to alcohol and healthy controls.

Overall, the current study is aligned with the bulk of the literature examining hippocampal volume abnormalities demonstrating that the hippocampi are particularly sensitive to the teratogenic effects of alcohol exposure during development. Additionally, these teratogenic effects hindering development seem to endure into childhood, long after the initial insult and exposure has ceased. This indicates that the hippocampus is unable to compensate for or recover from the effects of alcohol exposure in utero resulting in permanent neuronal loss that is sustained over childhood into young adulthood and perhaps over the lifespan.

Memory Retention

The final hypothesis derived from my first aim was to investigate whether higher levels of PAE were associated with poorer neutral declarative memory retention as measured by the story and list learning WRAML-II subtests. Retention is a behavioural proxy for memory consolidation as it measures the amount of information lost or gained after a period of time, in this case sleep, implicating its role in the strengthening of encoded information. Results pertaining to the retention of story-related information were entirely consistent with the hypothesis whereby individuals with higher levels of PAE had worse retention for this task. The

analysis showed that individuals with a diagnosis of FAS/PFAS retained significantly less information relating to the story task than healthy controls with those heavily exposed to alcohol trending towards the same pattern. The between-group finding held even when controlling for SES, sex and current cigarette use, that may have influenced the relationship, because each one of these factors was associated with the retention of story information. This highlights that regardless of education and occupation, identified sex or current smoking habits individuals with FAS/PFAS had the poorest story retention. The data supported the same pattern of association when considering the degree to which an individual was exposed to alcohol in utero: even after adjustment for multiple correlations, the association between dose-related PAE and story retention remained significant illustrating that higher doses of in utero exposure were worse for the retention of story-related information. This highlights that PAE robustly contributes to memory consolidation disruptions for this task. Nevertheless, contrary to the hypothesis the same pattern was not observed for list retention, which was not associated with PAE.

Previous literature examining declarative memory performance in individuals with PAE has not focussed on overnight consolidation and therefore, measures of overnight retention. Instead, studies have focussed on immediate and short-term delays in recall with some examining memory retention over the short delay period. Research has predominantly focussed on children and young adolescents and the use of the CVLT-C or CMS to assess declarative memory.

Most literature has found consistent deficits in verbal learning and recall in those with higher PAE compared to those with mild or no exposure (Crocker et al., 2011; Gross et al., 2018; Lewis et al., 2015; Mattson & Roebuck, 2002; Willoughby et al., 2008), with most results suggesting these retrieval deficits arise from problems encoding, although some point to

difficulties employing executive strategies (Lewis et al., 2015). However, inconsistent results have been reported for retention typically assessed through an adjustment method of controlling for initial or overall learning when assessing delayed recall. This is somewhat different from the method of the current study which assessed the percentage of words recalled after sleep in relation to those learnt in the final trial before sleep, accounting for prior learning in a different manner. For example, Crocker et al. (2011) and Willoughby et al. (2008) found that retention was preserved for those prenatally exposed as they performed similarly to controls when adjusting for initial learning on the CVLT-C delayed recall component. This was echoed by Mattson and Roebuck (2002) who found that both children with FAS and those exposed to alcohol without the diagnosis did not differ in retention on CVLT-C. On the other hand, Gross et al. (2018) and Lewis et al. (2015) showed that those with higher PAE retained less information than non-exposed individuals after adjustment on the CVLT-C delayed verbal recall for overall learning and IQ, suggesting encoding failure did not contribute to these deficits. However, of the two cohorts examined by Lewis et al. (2015), this was only found for the Detroit and not the Cape Town Cohort. Importantly, the participants recruited to the Cape Town cohort reported by Lewis et al. (2015) are the same (aged 10 years) as those in the current study. Nevertheless, the findings of a retention deficit for Gross et al. (2018) and the Lewis et al. (2015) Detroit cohort may be as a result of larger sample sizes than previous studies and lower alcohol exposure possibly allowing for better encoding and teasing apart of retention difficulties otherwise masked by poor encoding.

The CMS has also been used in studies examining verbal learning, although these results have also been inconsistent. Not related to retention, one study found deficits only in word-pair recall over short and long delays (Willford et al., 2004) while another observed worse immediate

and delayed recall in both word-pair and story subtests in those with FASD (Willoughby et al., 2008). Additionally, Willoughby et al. (2008) found that those with PAE performed worse when assessing retention for the word-pair task, though story retention was not reported. Thus, very little information is available on how those with PAE consolidate story-related information as opposed to list-learning or word-association tasks. A review of 23 studies examining verbal memory in samples of children and adolescents, also suggested that of the handful of studies accounting for retention, it has been intact in most instances even when accounting for encoding or learning deficits in individuals with PAE (du Plooy et al., 2016). This, alongside studies reporting altered retention in PAE, demonstrate that retention is not strongly influenced by encoding, unlike retrieval. Any problems with retention must therefore stem from processes specific to consolidation.

The lack of results found for the list-retention task in the current study does align with literature assessing word-list retention, albeit only in the short-term as opposed to overnight. This could be expected given that the CVLT-C task is very similar to the WRAML-II verbal learning task. Additionally, the current results align with the participants' earlier childhood assessment using the CVLT-C whereby no short-term difference in retention was revealed (Lewis et al., 2015). This may point to a similarity in the consolidation process of list material during periods of sleep and wake for individuals with PAE.

However, the results for list retention clearly diverge with respect to the story retention task whereby those with heavier PAE performed worse than controls, with the same trend for non-diagnosed but exposed individuals. Unfortunately, no studies have analysed or reported results related to story retention from tasks that were assessed. The clear overnight retention deficit for story-related information specifically reflects deficits in mechanisms of sleep

consolidation processes for this task and indicates that consolidation may differ between the list-learning and story tasks. The deficit, seeming to arise from in utero alcohol exposure, is specific to the retention of story-related information.

Speculatively, the reason for this discrepancy in consolidation performance between the two verbal declarative memory tasks may be due to the task structure and brain regions involved in the encoding and subsequent consolidation of that information. As is well-established, memory traces formed during encoding are known to be 'replayed' during sleep-dependent consolidation through specific coordination of oscillations (Klinzing et al., 2019). Thus, how the information is encoded plays a role in its consolidation. The list learning task comprises of everyday words representing isolated pieces of information. Brain regions associated with the learning and long-term memory of list-related information on the CVLT, and related tasks, have shown activation in the Papez circuit and left or bilateral medial temporal lobes (Johnson et al., 2001; Schallmo et al., 2015). This was confirmed by Schallmo et al. (2015) when assessing brain regions associated with long-term memory encoding for a word-list task. They found activations in the hippocampal formation, mammillary bodies, subgenual anterior cingulate, insula and other medial temporal regions. Although the Papez circuit relies heavily on the medial temporal lobe structures and hippocampus, which we know to be affected in those with PAE, the preserved retention on the list learning task may be due to the fact that information processing is relatively isolated to this circuit and does not rely on more complex integration with other brain circuits. Put differently, for a processing task of this nature, the Papez circuit that includes hippocampal structures, can cope with regards to consolidation in similar ways to non-exposed individuals. In contrast, the encoding of story-related information has shown activation in the default mode network (DMN) as well as medial temporal regions (H. Lee et al., 2020). This network is more

widespread and neocortical than the Papez circuit and is mainly comprised of the medial prefrontal, posterior cingulate, and association cortices including the angular gyrus and precuneus which interconnect to other regions such as the hippocampus (Buckner et al., 2008). It is known for its role in autobiographical thinking, most active during rest (Buckner et al., 2008). However, the DMN has also been shown to be active during the encoding of narrative information and is important for predicting narrative events and integrating contextual information and relationships with respect to space, time, characters and their actions (H. Lee et al., 2020). Additionally, when prior context is required to understand an element of a story and an event unit is identified, the DMN is associated with activation in the hippocampus with stronger activation related to successful recall and concomitant DMN re-activation (Barnett et al., 2024; H. Lee et al., 2020). Furthermore, interactions between the neocortical DMN and hippocampus that occur at the beginning or middle of an identified story-event are harmful for consolidation and recall as the unit of information is broken up (Barnett et al., 2024). Thus, there is an important hippocampal-neocortical dialogue specific for the encoding and consolidation of narrative contextual and event-specific information which seems to be more impaired in individuals with PAE. Even though most brain regions described across both declarative memory tasks are affected negatively in individuals with PAE (Lebel et al., 2011), it may be that PAE affects the ability to distinguish story-event boundaries correctly or the more complex hippocampal-neocortical pathways are more disrupted or less able to accommodate for neuronal loss than those in the Papez circuit, because the processing of information is more complex. Additionally, it may be that in individuals with PAE the hippocampus is more encumbered when processing and integrating contextually related information and its coordination with neocortical regions is hindered compared to isolated, non-contextually associated information. Speculatively,

it may be inefficient and dysfunctional when processing and moving memory traces across broader neuronal pathways of the DMN if there are fewer neurons to aid that process efficiently and accurately. The increased forgetting for the story task in individuals with higher PAE also reflects their poorer Everyday Memory Questionnaire results as the task more readily resembles day-to-day declarative memory processes of the structured narration of human experiences (Agnihotri et al., 2019).

In summary, the analysis of the first aim was largely confirmative of the hypotheses that those with more PAE suffered from more fragmented SWS, had smaller hippocampal volumes and worse story memory retention compared to those with lower levels of exposure. However, contrary to the prediction dose-related PAE was not as strongly associated with these alterations compared to a diagnostic approach, apart from story retention which maintained a clear relationship to PAE regardless of whether it was classified diagnostically or through maternal reports. In addition, list retention was not related to PAE, although this aligns with previous research examining word-list tasks in PAE individuals. PAE seems to have significant and long-lasting CNS involvement affecting the brain, sleep quality and consequently memory retention understood to represent sleep-dependent memory consolidation. More specifically, the results suggest that PAE plays a role in affecting SWS quality rather than quantity, which has been shown to be the more important factor in SWS consolidation mechanisms.

The Role of SWS-Architecture, hippocampal volume and PAE in the consolidation of neutral declarative memory

Regarding the second aim, I wanted to investigate whether SWS macro- and or micro-architecture was associated with the consolidation of story and list-learning tasks. In addition, I explored whether there was an interplay between SWS, PAE and hippocampal volume that was influential in the consolidation processes of verbal memory. In other words, whether individuals with PAE who have smaller hippocampi as well as altered SWS would have poorer consolidation performance. This hypothesis stems from research demonstrating the negative effects of PAE on sleep and memory performance as well as its alterations to hippocampal development which is a central structure to memory consolidation during sleep.

Story Retention

SWS micro-architecture. The association between SWS micro-architecture and the consolidation of story-related information is largely consistent with the literature examining consolidation through the framework of the *active systems theory*, although historically this has not been specific to story tasks but rather word-pair associates (e.g. Mölle et al., 2011). Story retention was strongly associated with SWS micro-architecture, specifically that of fast spindles. This association was specific to spindle duration, coupling percentage and coupling strength. The results show that a specific pattern of spindle parameters promotes better consolidation for this task, namely, more frequent fast spindles that occur over a shorter duration and couple over a more diverse spread of the SO wave.

Spindle Duration. The results highlight the importance of fast spindle duration for the consolidation of story information. They suggest that shorter bursts of fast spindle activity are the most beneficial spindle mechanism to consolidate contextual information. Spindle duration

has previously been associated with consolidation processes, though often to a lesser extent than other parameters (e.g. frequency and power) and typically only with procedural memory (Kumral et al., 2023). A meta-analysis attempted to determine the effects of spindle duration on memory and found that other features of spindles, such as frequency and power had greater memory consolidation benefits over duration (Kumral et al., 2023). There are a few studies showing some benefit of spindle duration for memory consolidation, but the findings show an inconsistent pattern of results. For example, favourable performance on a motor sequence learning task was associated with longer spindle durations during combined N2 and SWS compared to the control task (Morin et al., 2008), which was echoed for a pursuit rotor task, though only for spindles generated during N2 sleep (Fogel et al., 2007). However, other studies using the same procedure as the former did not find that spindle duration was associated with task performance (Barakat et al., 2011, 2013). Furthermore, spindle duration, whether increased or not, was not associated with measures of consolidation of the task (Barakat et al., 2011, 2013; Morin et al., 2008). Nevertheless, Tamaki et al. (2008) did find that greater N2 fast spindle duration during the learning night was associated with improvement on a mirror tracing task after overnight sleep. However, the small sample calls for the results to be interpreted cautiously. Altogether, there is some evidence that spindle duration, in some studies related to fast spindles, is involved in processing procedural tasks, however, it is not clear if this is the case for declarative memory or specific to spindles emerging from SWS.

Spindle duration has not been readily reported or associated with measures of declarative memory. However, some studies use ‘spindle activity’ or ‘SpA’ in relation to declarative consolidation which is a value derived from both spindle duration and amplitude, averaged across each epoch of the designated sleep stage being assessed, that reflects spindle intensity

(Schabus et al., 2004). In the meta-analysis SpA had the smallest effect out of all spindle characteristics (Kumral et al., 2023) which highlights the lesser significance of spindle duration when combined with amplitude, which typically has a strong association (Kumral et al., 2023; Ng et al., 2024). However, in some cases SpA, derived from N2 sleep, has shown clear associations with retention for declarative tasks, such as word-pair associations (Schabus et al., 2004). Nevertheless, from the literature on declarative memory, it seems that spindle duration is not generally reported in planned associations with declarative tasks, perhaps due to an absence of significant findings or a lack of theory underpinning its significance, despite associations revealed in procedural research. Moreover, it may be that the salience of fast spindle duration in consolidating verbal tasks has been missed given that a) most studies neglect or combine SWS with N2, b) do not classify spindles into fast and slow subtypes and c) do not include story-related tasks. The current findings provide insight of a clear role for shorter fast spindle duration in the consolidation of contextual information which contrasts with the beneficial nature of longer durations for procedural tasks and the lack of findings reported for declarative literature.

Speculatively, shorter durations may be more beneficial in some contexts as the faster oscillation may enhance the strength of memory traces through permitting the occurrence of more frequent and well-timed coupled spindles. A proportion of spindles occur in time to the initial firing of cortically generated SOs, whereby the large-scale bursts of neuronal activity create the opportunity for consolidation to occur by heightening plasticity (Fernandez & Lüthi, 2020). Plasticity refers to the ability of neuronal synapses to adapt to incoming signals by strengthening or weakening connections to other neurons due to changes in ion channels and receptors (Fernandez & Lüthi, 2020). The SO activates spindle activity through corticothalamic tracts which in turn entrain hippocampal ripples that convey memory-related information back to

the cortex for long-term storage (Fernandez & Lüthi, 2020). In addition, spindles tend to occur during specific phases of the SO wave during the periods of enhanced plasticity (Fernandez & Lüthi, 2020). Specifically, fast spindles reliably couple to the SO wave during its up-state which has been strongly associated with improved consolidation (Ng et al., 2024). Both increased coupling events as well as ensuring optimal timing during the SO are integral to the process of consolidation (Ng et al., 2024) which may be driven by shorter bursts of spindle activity. The unfavourable effects of longer spindles for consolidation may stem from them being less likely to occur over optimal phases of the SO that align with neuronal windows of plasticity beneficial for consolidation (Fernandez & Lüthi, 2020). For example, Eszopiclone has been shown to reduce the amplitude of SO waves which was associated with reduced coupling strength (Mylonas et al., 2020). A reduction in coupling strength illustrates increased variation in the timing of each coupling event and is typically detrimental to consolidation giving that more coupling events are mistimed (Muehlroth et al., 2019). Although spindle duration was not examined in relation to this finding, it could be that the weaker SOs resulted in longer and consequently suboptimally timed spindles (Mylonas et al., 2020). In support of this conjecture, findings from an *in vivo* study examining the brains of cats demonstrated that the administration of weaker cortical inputs allowed spindles to persist for longer highlighting that spindle duration is governed by cortical input (Bonjean et al., 2011). Therefore, longer spindles may be reflective of inadequate cortical inputs via SOs which consequently affects their timing.

Shorter spindles may be better suited to occurring and transmitting their parcels of information during beneficial SO phases while longer spindles may not adequately overlap with the window to transmit the entirety of their information parcel, hindering consolidation. As shorter spindles may be more likely to occur during the phases promoting plasticity, the

likelihood of successful coupling events occurring would increase benefitting retention whilst the opposite would be true for longer spindles (Ng et al., 2024). Considering the procedural literature, perhaps the advantages associated with spindle duration change depending on the type of information and brain areas involved in its consolidation. For the consolidation of story-related information, which has not been adequately explored in the literature, it seems that shorter fast spindles during SWS benefit the strengthening of these memory traces. Nevertheless, it is also important to consider that most of the sample has been exposed prenatally to alcohol which may also explain the somewhat unexpected association between retention and spindle duration, perhaps pointing to an altered consolidation mechanism for these individuals.

Coupling Percentage. Corroborating with the established the literature, the present findings demonstrated the weak though advantageous role coupling percentage plays in consolidation (Ng et al., 2024). In particular, an increased number of fast spindles coupled to SOs benefitted story retention. Intuitively, as coupling events are associated with enhanced plasticity derived from the up-state of the SO, increased coupling events should therefore be associated with behavioural measures of consolidation. Indeed, that has been shown to be true although to a weaker extent compared to other coupling parameters (Ng et al., 2024). Akin to the literature examining spindle duration, coupling percentage is linked more closely to retaining procedural information and overall does not show differences when differentiating between fast and slow spindles (Ng et al., 2024). With the goal of examining the potential effectiveness of Eszopiclone to benefit memory in individuals diagnosed with schizophrenia, Mylonas and colleagues found that regardless of drug or diagnostic group, increased N2 coupling density overlying motor areas were associated with improved overnight consolidation of a motor learning task (Mylonas et al., 2020). Conversely, coupling percentage did not differ across

spindle types or memory conditions for a spatial water maze task, however, the authors attribute that lack of findings to choosing a nap compared to overnight sleep-design and a lack of counterbalancing across conditions (Bastian et al., 2022). Regarding the declarative literature, NREM fast spindle coupling density has specifically been associated with the retention of word-pairs for information encoded during one trial highlighting a preference in the brain to consolidate novel information (Denis et al., 2021a). Contradicting this, although an odour cue presented during SWS increased coupled spindles around the SO up-state, this was not associated with consolidation of an image-location task (Sánchez-Corzo et al., 2024). Although this study did examine central electrodes which are associated with increased incidence of fast spindles, they did not differentiate between fast and slow spindle coupling events.

The evidence highlights a positive, though tentative, association between coupling percentage and measures of consolidation. However, the weaker relationship may also have arisen due to the way coupling frequency is reported across studies with some reporting percentage and others reporting density (number of coupling events per minute). Therefore, it may be that reporting density does not capture the same phenomenon as percentage does, resulting in inconsistent findings. Furthermore, the lack of consistency in the chosen declarative tasks (spatial vs verbal) could result in the altered findings whereby the tasks likely employ slightly different consolidation processes. Indeed, the current finding related to a verbal story task aligns most strongly with those reported by Denis et al. (2021a) for the word-pairs. This highlights that verbal declarative tasks may benefit from the same underlying mechanism of consolidation; whereby increased coupling events of fast spindles encourage consolidation.

The current study provides evidence that the percentage of fast spindles coupled to an SO is important for consolidation of story-related information, to an extent stronger than the average

reported by Ng et al., (2024). This is expected given that more spindles occurring periods of heightened neuronal plasticity creates more opportunity for the cortex to receive hippocampal information (Fernandez & Lüthi, 2020). Thus, there are more transfers and inter-regional communication of story-related information.

Coupling Strength. The present findings align with the literature, highlighting a clear relationship between coupling strength and sleep-dependent consolidation (Hahn et al., 2020, 2022; Ng et al., 2024). However, the direction of the relationship in this study is inverse to what has typically been demonstrated, whereby lower fast spindle coupling strength and hence more diversity in the coupling phase is beneficial for the consolidation of story-related information.

Coupling strength or the precision with which spindles couple across SOs has been shown to be integral within the memory consolidation framework (Ng et al., 2024). It is a measure of the quality of SO-spindle coupling events rather than quantity as it considers the preferred coupling phase of all spindles and is indicative of their synchronisation (Hahn et al., 2022). The consistency with which spindles couple has been shown to increase from childhood into adolescence (Hahn et al., 2020) and subsequently into young adulthood in healthy individuals (Hahn et al., 2022). More precision in SO-spindle timing across spindles has also been associated with better retention of declarative tasks such as word-pair associations and spatial-learning (Hahn et al., 2020; Mylonas et al., 2022) and procedural tasks such as juggling and mirror-tracing (Hahn et al., 2022; Mikutta et al., 2019). These increases in coordination have also been noted as regionally specific in relation to the chosen task: more frontal synchronisation for declarative tasks (Hahn et al., 2020) and more synchronisation involving motor regions for procedural tasks (Hahn et al., 2022). Supplementing what has been described, Muehlroth et al. (2019) found that fast spindle coupling strength declines with age and it is this change that is

associated with poorer retention of scene-word pairs. Additionally, participants within the younger group who had more diverse fast spindle coupling had similar retention deficits to older participants. Nevertheless, not many studies have specifically examined fast spindles in this regard. While the majority of studies are congruent in their findings, there are a handful of studies that have reported no direct relationship between coupling strength and retention of word-pair associates (Weiner et al., 2024) and novel verbal metaphors (Halonen et al., 2021) in healthy individuals, suggesting some complexity in the relationship.

A novel study placing intracranial EEGs in the brains of epileptic patients has highlighted the vital role that well-timed coupling events play in entraining hippocampal ripples and their associated memory traces (Helfrich et al., 2019). Importantly, hippocampal ripples represent memory traces that have been tagged during waking for preferential sleep-dependent consolidation (Yang et al., 2024). The intracranial placement of electrodes in the medial temporal lobe structures allowed for the recording of hippocampal sharp-wave ripples (Helfrich et al., 2019). A bidirectional relationship was revealed confirming what previous studies have surmised, that prefrontal SOs play a role in initiating hippocampal activity through subcortical spindle pathways when the coupling events are more synchronous (Helfrich et al., 2019). Therefore, more precise coupling increases the probability of activating a sharp-wave ripple and ensuring that replay occurs during optimal cortical states. The transfer of information to the cortex was shown to peak after the ripple and a period of desynchrony then occurs between spindles allowing the information parcel to be assimilated into cortical regions for long-term storage (Helfrich et al., 2019). When coupling strength is weak it may affect both the likelihood of entraining hippocampal ripples as well as whether the cortex is primed to receive and integrate the information.

Although the current results are in support of a strong association between retention and coupling strength, they diverge from what has been established, instead outlining an inverse relationship whereby less consistently coupled spindles benefit consolidation. In this regard it may be important to consider that two thirds of the sample have experienced mild to heavy PAE which may have given rise to the abnormal association. Thus, an unusual association between coupling strength and retention for individuals with PAE may overshadow the typical association for healthy individuals as established in the literature. Indeed, atypical associations reflecting the current results, have been reported for individuals with ASD compared to typically developing children (Kurz et al., 2021). The authors observed that for children with ASD, the recall of critical lures for a gist memory task (also assessing declarative memory) was improved when fast spindle coupling was imprecise. The authors surmised that dysfunctional, lower amplitude SOs may play a role in the adverse association as they are integral to driving spindle events (Kurz et al., 2021). Other studies have demonstrated that lower amplitude SOs resulting from exposure to Eszopiclone resulted in imprecise SO-spindle coupling, although this did not affect consolidation performance but highlights the link between SO integrity and SO-spindle strength (Mylonas et al., 2020). The current study did not find between-group differences in SWA, delta or SO PSD, that would indicate their involvement in atypical spindle mechanisms.

However, given that SO amplitude was not specifically assessed it is unknown whether it was altered for those with PAE, contributing to uncoordinated spindles perhaps through longer spindle events as surmised earlier. Kurz et al. (2021) also proposed that the atypical relationship may be indicative of a spindle coordination system that has had adapted to atypical neuronal organisation due to ASD. It is a high possibility that neuronal damage resulting from PAE may

have lent itself to a similar re-organisation of spindle dynamics adapted to ensure consolidation takes places, which is critical for later memory retrieval.

A Modulatory Effect of Coupling Strength. Individuals with PAE who have smaller hippocampi and altered SWS did not experience poorer retention as proposed. However, there was an association between hippocampal volume and SWS architecture that explained the degree to which information was retained after sleep. Although this does not confirm a direct role of PAE it is important to tentatively consider its relationship to hippocampal volume, which was established in the first hypothesis, when interpreting the results. In addition, the observed association provides a further explanation for the atypical findings observed between coupling strength and measures of consolidation.

The results revealed that increased consistency in the timing of spindles for those with smaller left hippocampi was detrimental for their consolidation processes whilst it was unrelated to performance for those with larger left hippocampi.

The former association highlights that individuals with less neuronal tissue within the hippocampus benefit from spindles that occur imprecisely. This contradicts the literature and previous findings specifically relating reduced brain volume of the medial prefrontal cortex (Helfrich et al., 2018), thalamus and hippocampus (Muehlroth et al., 2019) to altered fast spindle properties such as reduced strength and power, which are typically associated with poorer consolidation. However, the previous studies were assessing normally ageing brains, with reduction in volume relating to this process. In the current study, a third of the hippocampi have been exposed prenatally to alcohol leading to deleterious neuronal changes during critical development periods. Thus, the inverse association may reflect developmental adaptations to

central nervous system damage. Once, again more of the smaller hippocampi may have resulted from PAE, skewing the association to be atypical.

Why might contextual consolidation for individuals with smaller hippocampi in this young sample benefit from imprecise fast spindles? Speculatively, other consolidation mechanisms may have adapted to compensate for a hippocampus with less functional capacity. A smaller hippocampus may be unable to receive steady cortical inputs via thalamic spindles lest it becomes overburdened. Precise and consistent spindle input in concert with an underperforming hippocampus may result in the emitted ripples occurring outside of the SO-spindle window of plasticity. Thus, reactivated memory traces may be inaccurately consolidated or not at all which would be detrimental to memory function, especially if irrelevant memory traces were consolidated during the windows of plasticity. The neocortex may have adapted to produce more uncoordinated fast spindles to ensure that mistimed ripples are more likely to be captured in another window of plasticity. Additionally, Helfrich et al. (2019) observed that cortical spindles typically alternate between periods of high synchrony and then lower synchrony every 3-6 seconds, with lower synchrony periods associated with more information transfer arriving from medial temporal regions. Therefore, for individuals with smaller hippocampi that may sporadically produce ripples, maintaining a more asynchronous cortical environment would allow the cortex to constantly be primed to capture irregular memory reactivations for long-term storage. However, this is likely not without consequence to other functions occurring during sleep.

The latter finding that consolidation is not associated with fast spindle coupling strength for individuals with larger hippocampi also diverges from what has primarily been shown, demonstrating that coupling precision may not be as important as perceived for all declarative

tasks. Kurz et al. (2021) also found that for typically developing children, gist memory retention was not associated with fast spindle coupling strength. However, they purported that this may have resulted from gist memory, which is more abstract in nature, depending on competing or independent consolidation mechanisms. The present finding may highlight that consolidating story-related information also relies on other spindle or sleep-dependent mechanisms for individuals with larger and likely optimally functioning hippocampi.

Taken together, these fast spindle properties likely work in tandem to consolidate contextual information. The results highlight that in order to consolidate contextual information, more frequent fast spindle coupling events and their associated information transfers are required which may arise from shorter bursts of spindle activity that have a greater chance of overlapping with periods of plasticity triggered by SOs. Furthermore, the precision with which the fast spindles couple requires more diversity, although this was particularly related to individuals with smaller left hippocampi. In these cases, speculatively, an adaptation to ensure ripple activity is integrated into cortical networks may be favoured to compensate for a smaller, and therefore, suboptimally functioning hippocampus. Although PAE was not associated with the relationship between coupling strength and left hippocampal volume in determining the degree of story-related consolidation, those with smaller left hippocampi were more likely to have PAE.

A Lack of Association with SWS Macro-Architecture, Depth and Continuity. Although, there is clear evidence highlighting the role of SWS micro-architecture for the consolidation of story-related information the findings stand apart from the literature highlighting the role of time spent in SWS (e.g. Takashima et al., 2006), SWS continuity (e.g. Djonlagic et al., 2021) and SWS-depth (e.g. Barham et al., 2016) in consolidation.

The findings highlighted that SWS quantity as well as its continuity were not integral for the consolidation of story-related information which relied more heavily on other aspects of its quality. Regarding quantity, previous evidence for the beneficial role of time spent in SWS has stemmed from word-pair tasks (e.g. Gais & Born, 2004) thus, it appears that retaining story-related information may not rely on this aspect of SWS. Moreover, it is interesting that poorer SWS maintenance, as measured through arousals, was not associated with story retention difficulties. Although the arousals differed between exposure groups, overall, the disturbances may not have occurred often enough to disrupt consolidation processes, and instead poorer retention arose from altered oscillation characteristics.

Aligning with what was observed for SWS quantity, the current study may be the first to show a lack of association between SWS-depth and story-related information given that this task has rarely been explored in the literature. Indeed, there is some evidence showing that increasing SWA specifically through transcranial direct current stimulation does not benefit sleep-dependent declarative memory (Bueno-Lopez et al., 2019; Paßmann et al., 2016).

List Retention

SWS Macro-Architecture. In contrast to the findings related to story retention, SWS macro-architecture was associated with the retention of information pertaining to isolated words. Specifically, SWS quantity was the most important for the consolidation of this task, with increased percentage of time spent in SWS benefitting retention. The importance of SWS quantity has been highlighted for the consolidation of declarative information (Barham et al., 2016; Marshall et al., 2006; Perrault et al., 2019; Takashima et al., 2006). This has largely been in relation to word-pair association tasks, akin to the WRAML-II word-list task, that demonstrate that retention of non-contextual verbal information benefits from SWS macro-architecture. Both

causal, through techniques increasing time spent in SWS (Barham et al., 2016; Marshall et al., 2006; Perrault et al., 2019), as well as correlational studies (Takashima et al., 2006) have highlighted this association. Thus, the results align with what has been demonstrated in the literature.

A Modulating Effect of SWS Quantity. The percentage of SWS also influenced how much information was retained across the FASD diagnostic groups, exposing an indirect relationship between PAE and consolidation for the task. The findings show that word-list retention for unexposed individuals benefitted from increased time spent in deep sleep while for exposed individuals it did not. This highlights that PAE may diminish the effectiveness of time spent in SWS for consolidation of this task.

Given that spindles, coupling events and SWS-depth were not associated with performance on this task, it seems that, at least for isolated words, time spent in SWS is not a proxy for the micro-architecture events included in this study. Instead, the findings point to a general benefit of longer time spent in this sleep stage for healthy controls perhaps related to other features of SWS that were not included (SO characteristics, slow spindles) or unable to be detected (e.g. ripples). For those with PAE, it could be that these characteristics are impacted by PAE resulting in SWS states that do not effectively prime the cortex for consolidation of the word-list task. Therefore, time spent in SWS may not aid consolidation in the same way as it does for healthy controls. Although the measures of SWS-depth and fast spindle events that were examined may not be associated with retention of the word-list task, this may have stemmed from the nature of the task itself.

A Lack of Association with SWS Micro-architecture. In contrast to the majority of literature examining associations between SWS-architecture and consolidation, SWS micro-

architecture (SWS-depth, fragmentation, spindles and coupling events) was not associated with list learning retention.

Speculatively, the isolated nature of the word-list task, with regards to how the information is presented for encoding, may not rely on the fast spindle-coupling mechanism as heavily as the story task. Stories contain multiple pieces of information that require storage in varied cortical regions (e.g. characters, locations, time sequence of events). It is also essential for these memory traces to be inter-connected as they are part of the same sequence of events to be remembered. This spread of contextual information across diverse brain regions may rely on fast SO-spindle information transfers that are detected by scalp EEGs as they traverse broader brain networks to consolidate the information. Conversely, isolated pieces of information in the word-list task do not require contextual linking across a range of brain regions and instead take place in more spatially condensed networks such as the Papez circuit (Schallmo et al., 2015) which also happen to be predominantly subcortical. Thus, this type of verbal information may not require wide-range transfers of information which are perhaps represented by scalp EEG spindle-coupling events. Instead, cortical-thalamic-hippocampal dialogue, evidenced through SO-spindle events that are associated with word-list tasks may be mostly subcortical in nature making them less likely to be detected using the current methods. These events may only be captured using an EEG with increased spatial resolution. Therefore, SWS is likely still integral for consolidation and may have been a proxy for undetected subcortical micro-architecture events related to the word-list task which may explain why SWS quantity remained important while its scalp-level cortical micro-architecture characteristics were not.

In addition, the lack of findings may have resulted from how the task was presented. Denis et al. (2021a) found that increasing the number of times information was encoded lessened

its association with fast spindle characteristics whilst information only presented once was preferentially encoded by these coupling events. Given that the current list is presented four times to enhance encoding perhaps its association with fast spindle events was dulled in contrast to the story which was presented once.

Although the word-pair tasks used in literature are similar to the WRAML-II task they also differ in their description as periods of 'intense declarative learning' (Gais & Born, 2004). During the procedures described in these studies, participants in the learning condition have been required to memorise as many as 336 word-pair associates which translates into about an hour of learning (Gais et al., 2002; Mölle et al., 2004, 2011). Spindles and their coupling events have then been more strongly associated with consolidation processes for individuals in the learning conditions. The word-pair association task is much more intensive than the 16-item word-list utilised by the current study. Therefore, it may be that the less intensive paradigm did not induce increases in SWS micro-architecture events in response to the task to enhance consolidation. Therefore, the value of SWS macro- as opposed to micro-architecture for word-list consolidation may be explained by the fact that SWS quantity may not be influenced by the intensity of declarative learning.

Lastly, a lack of association with SWS micro-architecture may have occurred as SWS oscillations that could be associated with a less intensive task were not measured (e.g. SO waves, ripples, slow spindles) and rather than fast spindles or coupling, play a greater role in the consolidation process for this task and considering they were not measured, their influence remains unknown.

Overall, the benefit of SWS quantity likely stems from characteristics that were unable to be detected due to the nature of consolidation for isolated verbal information and the scalp-level

EEG (e.g. subcortical coupling, ripples). However, the task itself possibly also contributed to the absence of associations with detected fast SO-spindle events.

The Influence of PAE, Hippocampal Volume and Other Covariates (SES, ICV, Alertness, Sex, Sleep Quality and Anxiety) on Retention.

PAE. Both measures of PAE (maternal reports and FASD status) were detrimental for the consolidation of story-related information, however, dose-related PAE was associated with worse retention outcomes for the task. Studies have not typically compared group and dose-related variables describing PAE in relation to retention. Even if children have been recruited using the maternal dose-related reports, they are typically grouped into exposed vs non-exposed (Crocker et al., 2011; Gross et al., 2018; Willford et al., 2004) or classified into FASD diagnostic categories (e.g. Mattson & Roebuck, 2002; Willoughby et al., 2008). Only Lewis et al. (2015) assessed whether continuous exposure was related to verbal memory. Despite showing detrimental effects of exposure on immediate and delayed recall, it was not assessed in relation to retention. The current contribution of maternal reports of PAE in the context of consolidation does contrast with my previous findings emphasising the importance of FASD status over that of dose-related exposure for aspects such as SWS arousals and hippocampal volume. It provides evidence that how one chooses to classify PAE has implications for how it may be related to the chosen outcomes which do not seem to be a one-size-fits-all. For story memory it appears that accounting for a dose-related effect, rather than effects of that exposure, is more relevant.

Explored in the previous section, a possible explanation for the lack of association between PAE and word-list material may be derived from the more isolated nature of the Papez circuit which may allow for the consolidation of word-list items to be preserved even when the brain has been exposed prenatally to alcohol.

Hippocampal Volume. The size of the left hippocampus was negatively associated with the degree of story-related information retained after the sleep interval, with larger hippocampi associated with worse retention. However, the significance of this relationship was tempered by the small effect. It is crucial to examine the current literature on this relationship within the context of children given that the current study uses measurements taken from that time period to determine consolidation capability in adulthood. Plentiful research has been conducted examining how the hippocampus is related to delayed recall over periods of wakefulness. Although this could partially represent consolidation, it does not account for both gains and losses of information which retention, as a measure, does. In a review of 25 articles within the literature Botdorf et al. (2022) found that when considering children, adolescents and young adults, larger hippocampal volumes are consistently advantageous for recall performance across an array of memory modalities. This has included hippocampal subfields such as larger hippocampal bodies for adults and tails for children (de Master et al., 2014). This is in support of the 'bigger is better' hypothesis whereby larger structures are favourable for memory processes as they represent maturation in brain development (Botdorf et al., 2022; Van Petten, 2004). However, there is another hypothesis which has also has some support. A previous review by Van Petten (2004), for which there were only two articles at the time specific to children, found the opposite pattern. This was speculated to be due to underlying developmental processes such as neuronal pruning which boosted neuronal efficiency and preserved vital connections (Foster et al., 1999). More recent articles have shown that smaller hippocampal subfields such as the hippocampal head (de Master et al., 2014) or dentate gyrus is beneficial for adults (Daugherty et al., 2017). On balance however, it seems that research typically supports the 'bigger is better' hypothesis throughout the human lifetime (Botdorf et al., 2022; Van Petten, 2004). Conversely,

pathologically small hippocampi seen in Alzheimer's (Van Petten, 2004) as well as in children with PAE are more detrimental to recall, likely reflecting the altered or deficient neuronal pathways that have been recruited in this process (Coles et al., 2011; Willoughby et al., 2008). The research specifically assessing retention of information in relation to regional brain volumes in scarce and has typically focussed on adults (e.g. Pohlack et al., 2014) and has supported the 'bigger is better' hypothesis for this process.

The current findings diverge from the notion that increased hippocampal volume during childhood preserves memory and instead finds that larger volumes are not favourable, although, this was not entirely convincing given the small effect. This result is perplexing; however, it could partially support the neuronal pruning hypothesis. From this perspective the advantageous association between smaller hippocampi and story memory among children with no exposure (which may extend to those with mild exposure) may mask the presumed association that smaller volumes due to pathological processes (PAE) are harmful to retention in moderate and heavily exposed children. It could be that less exposed individuals outweigh those with more exposure and those that happen to have larger hippocampi due to pending, or less successful neuronal pruning are disadvantaged regarding their consolidation of information. Nevertheless, this result does not fit with the findings from the extant literature and should be interpreted with caution, given its associated small effect. It does suggest that using childhood brain measurements to map onto young adult memory performance may not be reliable and that taking hippocampal measurement needs to be aligned in time with behavioural performance.

Regarding word-list retention, the absence of a relationship with hippocampal volume was not unexpected when considering the results examining story retention. It could be that childhood volume is not successful in predicting consolidation performance in adulthood when

assessed independently. Conversely, retaining isolated pieces information may not heavily rely on the hippocampus. Again, this may stem from how word-lists are encoded using the Papez circuit whereby other regions or a cluster of them are perhaps more pertinent for consolidation of the task. Moreover, it may be that volumes of specific hippocampal subfields are activated for this task and considering the entire region masks these potential specialties.

In demonstration of their relevance to retention all associated SWS architecture remained meaningful alongside SES, ICV, level of alertness, sex, pre-laboratory sleep quality and anxiety scores.

SES. SES was measured as a function of education and occupation and is known to have bearing on one's cognition, particularly memory (Chevalère et al., 2023; Ford et al., 2022; Piccolo et al., 2016). Often individuals living in lower SES settings lack access to educational resources during critical periods of childhood development such as good quality schooling, stimulating toys or books in the home which have been associated with poorer memory performance (Ford et al., 2022; Piccolo et al., 2016). Educational resources would determine the vocabulary one is exposed to as well as memorisation and narrative comprehension skills. The lack of such skills would influence one's memory performance, although this would influence encoding and subsequent retrieval, rather than consolidation per se. Regarding consolidation, memory performance of children in lower SES environments may also be affected by disrupted sleep, which they experience more frequently than individuals from higher SES backgrounds (Buckhalt et al., 2007). In this sample, participants from lower SES backgrounds are more likely to experience exposure to more dangerous or frightening sleep disruptions as well as crowded sleeping areas (Correia et al., 2024; Ford et al., 2022). Thus, the finding that lower SES is more detrimental to retaining story-related information does align with the literature.

ICV. ICV is known to be associated with cognitive functioning, however the direction of the association, that smaller volumes are beneficial for consolidation of stories was unexpected. Typically, larger ICV is better for cognitive functioning (MacLullich et al., 2002; McDaniel, 2005; Royle et al., 2013; Rushton & Ankney, 2009). On the other hand, smaller ICVs are more pathological resulting in poorer cognitive performance such as in children and adults who were born at a low birthweight (de Kieviet et al., 2012). For the current study, these ICV measurements were taken during childhood. Therefore, the unexpected direction may be indicative of non-pathological neuronal pruning at the age of assessment, which is beneficial for their development and later cognition, resulting in the alternative direction in the association (Foster et al., 1999).

Alertness. Additionally, higher subjective alertness measured just before administering the declarative memory tasks for the first time also promoted story retention. It is important to capture one's subjective alertness before encoding takes place as this has an influence on one's executive processes such as attention which influences one's ability to encode information for subsequent consolidation. Increased alertness points to a better ability to attend to and encode the new information, especially for the story task which requires contextual and event-boundary encoding. Subjective measures of alertness, a substitute for physiological arousal, does predict performance on measures of attention gleaned through working memory tasks (Bermudez et al., 2016). Furthermore, poorer performance on working memory tasks which require attention are associated with worse performance on declarative memory tasks (Lum et al., 2015).

Sex. It was found that individuals identifying as male performed significantly worse than individuals identifying as female on the story task. Studies have found that females tend to perform better on measures of verbal episodic memory than males which has remained stable

over time, though this may be partially influenced by publication bias (Hirnstein et al., 2023). Nevertheless, this could explain the finding and provides evidence that females perform better on measures of consolidation for contextual information in comparison to males.

Sleep Quality. Average sleep quality showed an unexpected trend of worse subjective sleep prior to arriving at the laboratory predicting better word-list consolidation. Typically, poorer sleep quality is associated with worse measures of declarative consolidation as it hinders this process (Backhaus et al., 2006; Daurat et al., 2008; Djonlagic et al., 2021; Gu et al., 2023). However, this measure was taken before participants arrived at the laboratory and it is known that one of the mechanisms of sleep is to maintain neuronal balance by allowing neurons to recuperate (Dijk, 2009; Hejazi et al., 2024). Often this is through re-bound sleep in the nearest sleep period. Due to the consistently disrupted sleep experienced by the sample in their home environment, a longer period of re-bound sleep may have occurred to see this effect in night two (Correia et al., 2024; Lipinska & Thomas, 2017). Following this, perhaps participants who had poor subjectively rated sleep prior to arriving at the laboratory experienced more of a homeostatic drive to sleep, resulting in more restful sleep at the laboratory which aided consolidation. It has been shown that increased homeostatic drive to sleep, measured through sleep-depth bands (SWA, delta and SO), is associated with better retention of information (Huber et al., 2004; Marshall et al., 2006). A less disruptive sleep environment may have also worked in conjunction with the increased drive to sleep to promote word-list consolidation (Lipinska & Thomas, 2017).

Anxiety. Anxiety scores did follow the expected trend whereby increased symptoms of anxiety, as reported using the BAI, predicted poorer retention of the word-list information. Increased state anxiety has been associated with more disrupted sleep such as longer SOL

(Horváth et al., 2016). While both increased state and trait anxiety have been associated with reduced N2 and SWS which are implicated in consolidation (Horváth et al., 2016). In addition, individuals with severe anxiety and hyperarousal symptoms associated with a diagnosis of post-traumatic stress disorder (PTSD) as well as those who are trauma exposed have been shown to experience poorer verbal memory consolidation due to disrupted learning processes as well as fragmented sleep (Petzold & Bunzeck, 2022).

Summary of Story and List Retention Findings. In summary, the retention of story and word-list tasks seems to be highly distinguishable in this sample. Consolidation of story information is closely tied to SWS micro-architecture (quality) while retaining isolated words benefits from SWS macro-architecture (quantity). Moreover, the micro-architecture associations with story retention tend to deviate from what has been established in the literature, perhaps illustrating that contextual consolidation requires different configurations of SWS oscillations than what is typical for other declarative and procedural tasks. Story-related information tended to favour shorter and more frequent fast spindles which, although only for those with smaller left hippocampi, required more sporadic coupling event timing. The latter most finding likely indicates an adaptive process of the brain to preserve consolidation within the context of a suboptimally functioning hippocampus. In addition, while story retention was directly associated with PAE, list retention had only an indirect relationship whereby it was revealed that only individuals without PAE benefited from increased time spent in SWS. Moreover, the hippocampus did not have a strong influence on the ability to retain either story or word-list information. The importance of SWS architecture, PAE and hippocampal volume for the consolidation of the tasks was highlighted through the inclusion of SES, ICV, alertness, sex, sleep quality and anxiety which were also integral to the process. Lastly, some elements have

clearly shown no associations to retention of these declarative tasks, particularly some fast spindle properties (e.g. frequency, power, coupling phase), SWS fragmentation and SWS-depth which adds to the literature which has previously highlighted their involvement. Although it was not observed that individuals with PAE who have smaller hippocampi as well as altered SWS have poorer consolidation, the findings do contribute to the intricate relationship between SWS architecture, PAE and hippocampal volume in relation to consolidation processes of distinct verbal memory tasks.

Limitations and Future Directions

Limitations

It is important to acknowledge that there are limitations to the current study which must be considered when interpreting the results and contemplating future recommendations for research.

Recruitment. Firstly, as is common in research examining clinical populations, recruitment of participants with PAE was challenging, specifically individuals with a diagnosis of FAS. Although they belonged to a longitudinal study and had participated in previous research this was the first study that consent from a parent or guardian was not required as they were of consenting age. Consequently, there was a lower rate of participation in this group than previous years. Furthermore, as FAS is the most severe diagnostic category there are fewer individuals with the diagnosis within the cohort compared to the other exposure groups. Overall, this led to the very small FAS sample (n = 6) which needed to be combined with individuals with a diagnosis of PFAS for more accurate between-group comparisons. However, the lack of findings for some results pertaining to task consolidation or the involvement of SWS characteristics may potentially be explained by an inability to compare four exposure groups. Combining FAS/PFAS

may have suppressed how severe PAE affects sleep and memory. Future research should focus on recruiting more individuals with a diagnosis of FAS, although this limitation is likely to influence samples globally.

Substance Use. Second, there was a high rate of both marijuana and alcohol consumption within the cohort. These substances present as potential confounds, because they are known to independently influence sleep and consolidation. It was impractical to exclude participants based on use of these substances as doing so would have negatively impacted enrolment. Nevertheless, neither marijuana or alcohol use differed between exposure groups, nor were they associated with dose-related PAE or measures of retention. From this assessment, it is unlikely that use of either of these substances influenced the outcomes of the results. Additionally, given that PAE is associated with a high incidence of substance use as a result of mental health challenges, adverse childhood experiences and increased risk-taking behaviours (Dodge et al., 2019), it was unlikely that we would have been able to recruit a sample that abstained from all substances.

Childhood Brain Measurements. Third, I was only able to use prior measurements for hippocampal volume and ICV obtained during late childhood (Biffen et al., 2020). Although childhood hippocampal volume was related to the hypotheses it would be more salient to associate sleep and consolidation measures to current brain measurements. The brain undergoes many developmental changes to volume and connectivity throughout puberty and young adulthood which are important to consider in relation to consolidation processes and are not reflected in the childhood measurements (Botdorf et al., 2022; Van Petten, 2004). Moreover, measurements from childhood may not capture how alterations to the adult brain, due to PAE, are related to consolidation mechanisms. The use of hippocampal volumes stemming from pre-

puberty may explain the scarce, weak and often absent associations with retention and SWS oscillations as well as the non-significant three-way interaction between PAE, hippocampal volume and SWS-architecture, which was highly suspected. In further contribution to the lack of associations, the younger measurements may reflect better hippocampal functioning, before subsequent, perhaps deleterious, developmental processes, for individuals with PAE. Although the current associations partially support the role of the hippocampus in consolidation mechanisms in young adults, these effects may have been stronger and more abundant if the current volume was accounted for. This highlights the need to capture current volumes for accurate interpretations to be made about consolidation. Future studies examining sleep and memory in young adults with PAE should obtain current estimates of hippocampal volume and ICV to more accurately determine how the hippocampus is involved in sleep and consolidation mechanisms in adulthood in this population.

SWS Micro-Architecture Measurement. Fourth, measuring techniques for spindle events and SWS-depth may have also contributed to some of the null findings in the analysis.

Regarding fast spindle frequency, which has previously been associated with consolidation (Kumral et al., 2023), I used individualised peak sigma frequencies to classify fast spindles (Denis et al., 2021a, 2021b) rather than a defined range, which has typically been used in earlier research. This method ensures the peaks coincide with the frequency range that likely has the highest occurrence of spindles. Therefore, the study may provide evidence that when accounting for individualised peaks rather than a predetermined range, frequency becomes less important for retention. Conversely, the study may have missed the association if lower amplitude fast spindles outside the range were overlooked.

Increased fast spindle power and coupling phases centred around the SO up-state have both been strongly tied to consolidation processes (Kumral et al., 2023; Ng et al., 2024). Given that fast spindles are reported to be more prevalent over central electrode sites (Fernandez & Lüthi, 2020) and many works have used central regions to successfully detect their activity in relation to consolidation (Denis et al., 2021b; Gais et al., 2002; Mölle et al., 2004, 2011), I chose to use only central derivations. However, this may have resulted in omitting less frequent but perhaps more meaningful frontal fast spindles. Indeed, Ng et al. (2024) highlighted that frontal channels may be more relevant to capture both spindle sigma amplitude (used to calculate power) and coupling phase associations with consolidation performance (Ng et al., 2024). For example, although fast spindle coupling phase was initially associated with story retention, this finding disappeared in later analyses perhaps due to the focus on central derivations. This is because coupling phase has been shown to decrease away from the up-state with more posterior derivations with frontal fast spindles occurring very close to the up-state while central and parietal spindles shift down. Fast spindles occurring at or very near to the up-state phase are the most beneficial for consolidation (Ng et al., 2024). In addition, although the current phase results were similar to Cox et al. (2018), they were lower on the slope than typical for central regions (Ng et al., 2024) perhaps further contributing to the non-significant findings.

Secondly, I chose to assess SWS-depth in units of relative PSD (uV^2 / Hz) which controls for both individual differences in frequency resolution and variation in skull thickness and gyral folding (Cox & Fell, 2020; Cunningham et al., 2021; Denis et al., 2021b). Although, this technique accounts for these sources of variation it may have led to the null findings between SWS-depth and consolidation. There is substantial evidence highlighting the importance of SWA, delta and SO power in declarative memory consolidation (Barham et al., 2016; Marshall et

al., 2006, 2004; Ngo et al., 2013; Ngo & Staresina, 2022), however the current study may be one of the first to show that when accounting for these sources of variation these established effects are diminished in relation to verbal memory tasks.

While these measurement choices for fast spindles and SWS-depth are justified, and some a priori decisions regarding an analytic focus have to be made, there is at present no gold-standard protocol to measure these variables and a high degree of variation in the literature. Future studies should aim to analyse frontal derivations as well as compare relative and absolute PSD and power estimates in relation to consolidation for declarative tasks. Furthermore, perhaps gold-standard protocols should be investigated to ensure better comparison across studies in the field.

Future Directions

Given the absence of research into the relationship between sleep and cognition in individuals with PAE, there are ample avenues for future research. A key takeaway from the present results is the potential differences in brain regions associated with consolidating distinct verbal declarative tasks as well as how retention of these tasks is differentially affected by PAE with story-related information being heavily, negatively impacted. It would be useful to explore encoding and retrieval patterns using functional MRI to determine which areas of the brain are more active during these processes in individuals with and without PAE. Additionally, calculating the difference in areas activated at these timepoints can be assessed to determine which areas are preferentially involved in consolidation and whether this deviates for each task across exposure groups (Schallmo et al., 2015). Both functional and structural information can be obtained simultaneously, allowing for current brain measurements to be associated with consolidation and sleep measurements. Furthermore, one could consider more ecological and

intensive tests of declarative memory for this exploration. Perhaps a future study could explore the story-related deficit in-depth using audio-visual and/or conversational narrative structures reflective of everyday memory events while more intensive word-list paradigms could be employed to tease apart deficits in retention of isolated verbal information for individuals with PAE given the mixed findings related to the less intensive CVLT-C and CMS.

In conjunction, objective PSG recordings could be used to gather information pertaining to both N2 and SWS macro- and micro-architecture during the time between encoding and retrieval as N2 sleep has also been implicated in consolidation processes. It could be useful to understand whether dysfunctional micro-architecture occurs more frequently during N2 sleep which more potently contributes to consolidation difficulties in either task for individuals with PAE. Moreover, it could be that hippocampal alterations are more strongly linked to perturbations within this sleep stage for individuals with PAE. Furthermore, although they are typically not associated with consolidation it could be useful to examine slow spindle events. They may provide nuance in terms of where consolidation deficits are occurring for those with PAE as their deficits in retention may result from dysfunctional slow spindles.

Regarding SWS-depth the odds ratio product (ORP; Younes, 2023) could be utilised. ORP is a validated, continuous measure of sleep-depth derived from all sleep spectral power bands per epoch with higher values indicating lighter sleep and an increased chance of arousal (Younes, 2023). As a measure of sleep maintenance, ORP may be a more salient predictor of consolidation than individual power bands in the context of PAE. This is because PAE is associated with more sleep fragmentation which is known to be harmful to consolidation processes. Accounting for the probability of fragmentation within the sleep-depth measure and overall ‘wakefulness’ for each sleep stage may provide more nuance for how sleep-depth

contributes to consolidation difficulties in exposed individuals that is not captured when assessing the power bands separately. A handful of studies have highlighted ORP's association with cognition (Beaudin et al., 2024; Gu, 2021). Perhaps future studies can compare ORP, PSD and power band measurements in individuals with PAE and how they relate to measures of consolidation to determine whether ORP is a more useful measure.

The findings also provide insight into the complex interactions between SWS oscillations and brain structures that occurs for consolidation to take place including new relationships associated with story-related information and reduced hippocampal volumes. Future research may endeavour to explore (a) whether fast spindle duration is reliably related to the consolidation of story tasks and (b) whether the link between dampened SOs and reduced coupling strength is bound by longer fast spindles which are derived from weaker SO inputs and (c) whether this is associated with consolidation. Lastly, it may be useful to use an EEG with higher spatial resolution to capture hippocampal ripple activity in individuals with pathologically and non-pathologically smaller hippocampi (i.e. exposed vs unexposed individuals) to determine whether ripple activity is more sporadic for the latter or whether smaller hippocampi generally result in altered micro-architecture dynamics and whether these dynamics are what was purported. Furthermore, a higher EEG resolution would also be beneficial to capture more nuanced spindle and ripple associations, which may be useful in association to word-list task performance to determine whether retention of this information is associated with more subcortical SWS oscillatory activity.

Future studies could also diverge from correlational designs typically used to assess consolidation performance in individuals with PAE and instead utilise an experimental design to illicit causation. One could assess whether manipulating SWS oscillations using invasive or non-

invasive techniques benefits consolidation for those with PAE in the same manner as those without exposure.

Summary and Conclusion

This research provides novel insights into (a) sleep-dependent declarative memory consolidation and (b) the longstanding impacts of PAE on key components involved in this process. The findings were confirmative of previous research into FASD regarding their preserved SWS macro-architecture, while newly demonstrating that individuals with FAS/PFAS have specific deficits in SWS maintenance. A more severe FASD diagnosis was also prominently associated with childhood hippocampal abnormalities. While word-list consolidation was intact across exposure groups, mirroring previous short-term daytime retention studies, deficits were evident for the story task which historically has not often been utilised in either FASD or declarative memory research. This illustrated a clear consolidation deficit related to sleep-dependent processes for story information, highlighting that contextual information is more challenging to retain for individuals with PAE in comparison to isolated words. This task may, in fact, better reflect subjective memory complaints as it is a more ecological test of memory.

Importantly, the story task was intimately linked to fine-grain elements of sleep such as SWS micro-architecture which underpin its quality, although in ways that differed from what has previously been established. This provided evidence for mechanisms that are specific to consolidating narrative information and in the case of coupling strength, reflective, speculatively, of how the brain may rearrange oscillatory activity when hippocampal regions function suboptimally. On the other hand, only individuals without PAE benefitted from increased time spent in SWS for the word-list task.

The findings highlight the importance of SWS macro- and micro-architecture for the consolidation of declarative information. Furthermore, they illustrated that although story and word-list tasks both encompass neutral verbal declarative information, their processing during SWS is governed by different consolidation mechanisms in addition to being differentially affected by PAE. While word-list information was intact after overnight sleep, it appears that the deleterious effects of PAE are more evident in contextual story-related tasks requiring information to be stored and assimilated into widespread brain regions.

While there are trials in progress to assess the ability of supplements such as choline to mitigate the effects of PAE on the developing fetus, the current research provides guidance for future interventions that target sleep for individuals currently living with PAE as well as other neurodevelopmental disorders for which there are no specific sleep interventions other than those related to sleep hygiene. While SWS maintenance would be important to leverage, it is less associated with these memory tasks, therefore, methods that target spindle activity would be more beneficial to improve sleep-dependent consolidation. For example, non-invasive techniques such as targeted reactivation could be used to generate better-timed coupling events for consolidation. Consequently, it would be useful to explore whether the sporadic pattern of coupling observed for individuals with smaller hippocampi is indeed more beneficial for these individuals using this approach as well as explore this in individuals with larger hippocampi. In addition, perhaps medications enhancing spindle activity could be better researched and eventually prescribed to individuals with more severe memory difficulties to alleviate some of their memory difficulties, and therefore, their cognitive burden (Leong et al., 2022). In addition, future strategies may target children who have PAE during late childhood when neuroplasticity is heightened to provide education surrounding memory techniques and the importance of sleep as

well as implementing the sleep interventions. Lastly, future studies may unravel sleep signatures specific to PAE which could be used as a biomarker of exposure level.

Overall, this pioneering study examining the complex interactions between PAE, SWS, brain structures and memory, highlights the enduring effects of PAE on these core biological functions and structures. It provides new insights encouraging exploration of sleep-targeted interventions given the nature of sleep as a modifiable factor, which is central to consolidation and results in stable and enduring memory function.

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Appendices

Appendix A

Comparisons to Parent Study

	Proposed Study	**Parent Study**
Study Aims	Investigating the associations between prenatal-alcohol exposure (PAE; both diagnostically and continuously from maternal measures), childhood hippocampal volume, slow-wave sleep (SWS) features and neutral declarative memory retention.	Investigating the associations between FASD, disrupted sleep architecture and cognitive and affective impairment
Study Hypotheses	1a) Those with higher PAE will spend less time in SWS, increased SWS fragmentation, have lower PSD in the delta, SO and SWA bands, reduced spindle density and coupling and altered spindle properties compared to those with mild or no PAE. 1b) Those with higher PAE will have smaller left and right hippocampal volumes compared to those with mild or no PAE. 1c) Those with higher PAE will have poorer neutral declarative memory retention for both story and word-list tasks compared to those with mild or no PAE. 2a) SWS macro and/ or micro-architecture will predict memory retention 2b) Those with PAE who have smaller hippocampi and SWS-related alterations will have poor memory retention after a period of sleep.	Young adults diagnosed with FAS or PFAS will experience more PSD-measured disruption of SWS and rapid eye movement (REM) sleep than healthy control participants. Young adults diagnosed with FAS or PFAS will show poorer retention of information across the sleep-filled delay than healthy control participants. The effects of FASD and PAE on memory consolidation will be mediated, in part, by specific disruptions to SWS. Participants with FAS or PFAS will show altered emotional reactivity to previously encountered valenced stimuli at post-sleep measurement relative to healthy control participants. The effects of FASD and PAE on emotional reactivity measures will be mediated, in part, by specific disruptions to REM sleep.
Data Analysis Plan	One-way ANOVAs and Kruskal-Wallis Rank sum tests will examine between-group	One-way ANOVAs will examine between-group differences on PSG

	differences on PSG measures of SWS features, hippocampal volumes and memory retention for both tasks. Relations between memory retention and SWS features will be examined using Pearsons or Spearman's correlations. Relations between continuous PAE and sample characteristics will be examined using Spearman's correlations. Linear regression models will examine a) features of SWS that are predictive of memory retention; b) whether SWS characteristics, PAE and/or hippocampal volume is predictive of memory retention 3) whether having PAE, smaller hippocampal volume and altered SWS influences memory retention.	measures including SWS percentage, REM percentage and sleep latency. Linear regression models will examine the relation of a continuous measure of PAE to the same outcomes. Relations between subjective sleep quality scores and objective PSD measures sleep quality will be examined using Spearman's rho. A one-way ANOVA will examine FASD diagnostic group differences in declarative memory retention. The correlation between PAE and declarative memory retention will be examined using linear regression. One-way ANOVAs will examine FASD diagnostic group differences in psychophysiological measures of change in heart rate from pre- and post-sleep measurement and in recognition accuracy associated with valenced images. The correlation of PAE with group differences in psychophysiological measures of change in heart rate will be examined using linear regression.

Appendix B

Hippocampal Volume Data

Neuroimaging assessment. Participants in the Cape Town Longitudinal Cohort were scanned at the Cape Universities Brain Imaging Centre using a 3T Siemens Allegra MRI (Siemens Medical Systems, Erlangen, Germany) when they were 9–11 years old (Meintjes et al., 2014). High-resolution T1-weighted images were obtained using a volumetric navigated (Tisdall et al., 2012) multi-echo magnetization prepared rapid gradient echo (MEMPRAGE) sequence. This sequence was optimized for analysis with FreeSurfer (van der Kouwe et al., 2008). Imaging parameters were: FOV 256 × 256 mm^2, 128 sagittal slices, TR 2530 ms, TE 1.53/3.21/4.89/6.57 ms, TI 1100 ms, flip angle 7°, voxel size 1.3 × 1.0 × 1.3 mm^3, acquisition time 8:07 min. Real-time motion tracking and correction by the volumetric navigator reduced artefacts resulting from motion. Automated segmentation and parcellation of the hippocampus were performed using FreeSurfer Version 6.0.0. Segmentations were visually checked for accuracy.

The citations in this paragraph can be found in Biffen, S.C., Warton, C.M.R., Dodge, N.C., Molteno, C.D., Jacobson, J.L., Jacobson, S.W., & Meintjes, E.M. (2020). Validity of automated FreeSurfer segmentation compared to manual tracing in detecting prenatal alcohol exposure-related subcortical and corpus callosal alterations in 9- to 11-year-old children. NeuroImage: Clinical, 28, 102368.

Appendix C

Sleep Diary

Record ID:

ID:

Date:

Examiner:

1. What time did you get into bed?
2. What time did you try to go to sleep?
3. How long did it take you to fall asleep?
4. How many times did you wake up, not counting your final awakening?
5. In total, how long did these awakenings last?
6. What time was your final awakening?
7. What time did you get out of bed for the day?
8. How would you rate the quality of your sleep?
    - Very Bad
    - Bad
    - Okay
    - Good
    - Very Good
9. Comments:

Appendix D

DOA

Record ID:

ID:

COCAINE

- True
- False

1. When?
2. Where?
3. How much?
4. How often?

AMPHETAMINE

- True
- False

1. When?
2. Where?
3. How much?
4. How often?

METHAMPHETAMINE

- True
- False

1. When?
2. Where?
3. How much?
4. How often?

THC

- True
- False

1. When?
2. Where?
3. How much?
4. How often?

OPIATES

- True
- False

1. When?
2. Where?
3. How much?
4. How often?

Please upload an image of the test.

Appendix E

Demographic Questionnaire

Record ID:

ID:

Date:

Examiner:

LIVING ARRANGEMENTS

1. Are you married?/ Is jy getroud?

- Single
- Married, living with spouse
- Living with partner as if married
- Separated
- Divorced
- Widowed

2. Who do you live with all or most of the time?/ Wie bly jy met vir die meeste tyd?

- Live alone
- Spouse
- Partner (i.e., boyfriend or girlfriend)
- Parent(s)
- Roommate(s)

- Other (specify)

2a. If other, specify:

3. Is there a second place you often stay? With whom do you stay there? / Is daar 'n ander plek waar jy partykeer bly? Wie bly jy daar saam met jou?

- No (Go to Q5)
- Alone
- Spouse
- Partner (i.e., boyfriend or girlfriend)
- Parent(s)
- Roommate(s)
- Other (specify)

3a. If other, specify:

4. How often do you stay in the place listed in Q3?/ Hoe gereeld bly jy daar?

- Days/week
- Days/month
- Days/year

5. Do you have any children?/ Het jy enige kinders?

(Enter number of children. 0 if no children)

How old are your children?/ Hoe oud is jou kinders?

Who takes care of your children most of the time? Wie sorg, die meeste van die tyd, vit jou kinders?

- I do (with or without spouse/partner)
- Spouse/partner does
- Child's grandparents
- Other (specify)
- If other, specify relationship (e.g., aunt, friend):

EMPLOYMENT

1. Are you currently employed?/ Werk jy nou?

- Yes
- No

If yes, what do you do?/ Wat doen jy by die werk?

Hours per week:

If no, what was your most recent job? Wat het jy onlangs vir werk gedoen?

Hours per week of most recent job:

When did this job finish?

2. Is the partner (spouse/boyfriend/girlfriend) you live with currently employed?/ Werk jou (man/vrou/girlfriend/boyfriend)?

- Yes
- No

- No current partner

If yes, what do they do?/ Wat doen hulle vir werk?

Hours per week:

If no, what was their most recent job?/ Wat het hulle onlangs vir werk gedoen?

Hours per week of their most recent job:

When did this job finish?

How many (full time equivalent) years of school has your partner completed?/ Hou veel jare skool het hulle klaar gemaak?

3. Does anyone else help support you financially?/ Is daar enige iemand anders wat jou finansiaal help?

- Yes
- No

How much of your support does s/he provide? (approximate percentage) Hoe veel ondersteuning gee hulle vir jou?

Who provides this support?

- Parents
- Other

If other, please specify:

What is his/her primary source of income?

How many (full time equivalent) years of school has s/he completed?

EDUCATION

1. How many (full time equivalent) years of school have you completed?

2. What was the name of the last school you attended?

3. Have you attended any college or training programs?

- Yes
- No

What college or training program?

What did you study?

How long were you enrolled in the program?

4. Did you attend any other college or training programs?

- Yes
- No

What college or training program?

What did you study?

How long were you enrolled in the program?

HEALTH HISTORY

1. Do you have any health problems?

- Yes
- No

What type of health problems?

1a. So in general, would you say your health is ...

- Excellent
- Good
- Fair
- Poor

2. Do you have any vision problems?

- Yes
- No

Describe your vision problems...

3. Do you have any hearing problems?

- Yes
- No

Describe your hearing problems...

4. Have you ever been told you have attention deficit/hyperactivity disorder (ADHD)?

- Yes
- No

Who told you?

Any medication?

- Yes
- No

Specify:

How old were you when you started taking it?

Are you still taking it?

- Yes

- No

How old were you when you stopped taking it?

4. Have you had any accidents/injuries which required medical attention?

- Yes
- No
    - Any broken bones?
    - Needed stitches?
    - Any burns?
    - Head injury?
    - Severe bruises?
    - Other injury?

If yes to any of the above, please describe:

a. What kind of injury was it?

b. How old were you at the time?

c. What medical treatment or tests were performed?

d. Were you hospitalized? If yes, for how long?

5. Have you had any seizures?

- Yes
- No

What was the cause of the seizure (e.g., epilepsy, car accident, febrile seizures, etc.)?

How old were you at the time?

Were any medications prescribed? (e.g., anti-convulsant drugs, Phenobarbital, Dilantin)?

Is s/he still taking it?

- Yes
- No

7. Do you have any of the following...

a. Heart problems

- Yes
- No

Age first detected?

Describe the problem and treatment.

b. Diabetes

- Yes
- No

Age first detected?

Describe the problem and treatment.

c. Kidney problems

- Yes
- No

Age first detected?

Describe the problem and treatment.

8. Have you ever been hospitalized for any reason (other than already noted above)?

- Yes
- No

Hospitalization 1:

How old were you at the time?

What was the reason?

Was surgery and/or any medical tests performed?

Hospitalization 2:

How old were you at the time?

What was the reason?

Was surgery and/or any medical tests performed?

Hospitalization 3:

How old were you at the time?

What was the reason?

Was surgery and/or any medical tests performed?

Hospitalization 4:

How old were you at the time?

What was the reason?

Was surgery and/or any medical tests performed?

Hospitalization 5:

How old were you at the time?

What was the reason?

Was surgery and/or any medical tests performed?

9. Are you currently taking any other prescription medications?

- Yes
- No

Prescription medication 1:

What medications are you taking?

What are the reasons?

Since when have you been taking this medication?

Prescription medication 2:

What medications are you taking?

What are the reasons?

Since when have you been taking this medication?

Prescription medication 3:

What medications are you taking?

What are the reasons?

Since when have you been taking this medication?

Prescription medication 4:

What medications are you taking?

What are the reasons?

Since when have you been taking this medication?

Prescription medication 5:

What medications are you taking?

What are the reasons?

Since when have you been taking this medication?

10. Have you taken any prescription or over-the-counter medication in the past 24 hours?

- Yes
- No

Medication in past 24 hours 1:

What was the name of the medication?

What dose?

Reason for medication?

What time did you last take it?

Medication in past 24 hours 2:

What was the name of the medication?

What dose?

Reason for medication?

What time did you last take it?

Medication in past 24 hours 3:

What was the name of the medication?

What dose?

Reason for medication?

What time did you last take it?

Medication in past 24 hours 4:

What was the name of the medication?

What dose?

Reason for medication?

What time did you last take it?

Medication in past 24 hours 5:

What was the name of the medication?

What dose?

Reason for medication?

What time did you last take it?

11. Do you have any special problems or illnesses not already discussed?

- Yes
- No

Describe those problems or illnesses.

EXAMINER COMMENTS ONLY

Appendix F

PSQI

Record ID:

ID:

Date:

Time:

Examiner:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

Die volgende vrae het te doen met jou gewone slaap gewoontes, maar slegs gedurende die afgelope maand. Jou antwoorde moet die mees akkurate antwoord aandui vir die meerderheid van dae en aande gedurende die afgelope maand. Beantwoord asseblief alle vrae.

1. During the past month, what time have you usually gone to bed at night?/ Gedurende die afgelope maand, hoe laat het jy gewoonlik gaan slaap in die aand? (BED TIME)
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?/ Gedurende die afgelope maand, hoe lank (in minute) het dit jou gewoonlik geneem om aan die slaap te raak elke aand? (NUMBER OF MINUTES)

3. During the past month, what time have you usually gotten up in the morning?/ Gedurende die afgelope maand, hoe laat het jy gewoonlik in die oggend opgestaan? (GETTING UP TIME)

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)/ Gedurende die afgelope maand, hoeveel ure se werklike slaap het jy per aand gekry? (Hierdie mag dalk anders wees as die hoeveelheid ure wat jy in die bed spandeer het.) (HOURS OF SLEEP PER NIGHT)

For each of the remaining questions, check the one best response. Please answer all questions. During the past month, how often have you had trouble sleeping because you . . . Vir elkeen van die volgende vrae, kies die een beste antwoord. Beantwoord asseblief alle vrae./ Gedurende die afgelope maand, hoe dikwels het jy moeilik geslaap omdat jy...

5a) Cannot get to sleep within 30 minutes/ Nie aan die slaap kan raak binne 30 minute nie

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5b) Wake up in the middle of the night or early morning/ Wakker word in die middel van die aand of vroeg in die oggend?

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week

- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5c) Have to get up to use the bathroom/ Moet opstaan om die badkamer te gebruik

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5d) Cannot breathe comfortably/Nie gemaklik kan asemhaal nie

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5e) Cough or snore loudly/ Hard hoes of snork

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5f) Feel too cold/ Te koud voel

- Not during the past month / Nie gedurende die afgelope maand nie

- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5g) Feel too hot/Te warm voel

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5h) Had bad dreams/Slegte drome het

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5i) Have pain/ Pyn het

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

5j) Other reason(s), please describe/ Ander rede(s), beskryf asseblief

How often during the past month have you had trouble sleeping because of this?/ Hoe dikwels gedurende die afgelope maand het jy moelik geslaap as gevolg van dit?

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

6. During the past month, how would you rate your sleep quality overall? Gedurende die afgelope maand, wat sou jy sê is jou algehele slaap kwaliteit?

- Very good / Baie goed
- Fairly good / Redelikgoed
- Fairly bad / Redeliksleg
- Very bad / Baie sleg

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?/ Gedurende die afgelope maand, hoe dikwels het jy medisyne geneem om jou te help slaap (voorgeskrewe of "oor-die-toonbank")?

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity? Gedurende die afgelope maand, hoe dikwels het jy dit moeilik gevind om wakker te bly terwyl jy bestuur, eet, of aan sosiale aktiwiteite deelneem?

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?/ Gedurende die afgelope maand, hoe moeilik was dit vir jou om genoeg entoesiasme te behou om dinge
gedoen te kry?

- No problem at all / Geenprobleemnie
- Only a very slight problem / Slegs 'n effense probleem
- Somewhat of a problem / 'n Redelike probleem
- A very big problem / 'n Baie groot probleem

10. Do you have a bed partner or room mate?

- No bed partner or room mate
- Partner/room mate in other room
- Partner in same room, but not same bed
- Partner in same bed

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

10a) Loud snoring

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

10b) Long pauses between breaths while asleep

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

10c) Legs twitching or jerking while you sleep

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

10d) Episodes of disorientation or confusion during sleep

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week

- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

10e) Other restlessness while you sleep; please describe

- Not during the past month / Nie gedurende die afgelope maand nie
- Less than once a week / Minder as een keer per week
- Once or twice a week / Een of twee keer per week
- Three or more times a week / Drie of meer keer per week

Additional Notes:

Appendix G

TLFB

Record ID:

ID:

Examiner:

Date:

SMOKING

1. Have you ever smoked cigarettes?
    - Yes
    - No
2. What age did you first try smoking cigarettes?
3. Do you currently smoke cigarettes?
    - Yes
    - No
4. How many cigarettes do you smoke per day or per week?

ALCOHOL

*The following is an excerpt from the alcohol portion of the interview. The same questions were asked for every day over the past month whereby the participant had consumed alcohol, going back one week at a time.

1. Have you ever drunk alcohol?
    - Yes

- No

2. When was the last time you drank beer (or other alcoholic drink)?

- Within the past week
- During the week before that
- 3 weeks ago
- Other (specify)

If other, specify:

In the past week, on what days did you drink?

- Friday
- Saturday
- Sunday
- Monday
- Tuesday
- Wednesday
- Thursday

Friday

a. Where were you? Who did you drink with? What was going on?

b. Did the group share bottles or boxes of wine? That is, did they pass it around so that everyone drank about the same amount?

- Yes
- No

c. How many people drank together?

Beer

- Corona
- Castle lager lite, Black Label, or Lion lager glass bottles
- Castle lager lite, Black Label, or Lion lager cans
- 660 ml quarts
- 750 ml quarts
- Other (specify)

Corona

Number of bottles:

Castle lager lite, Black label, or Lion lager

Number of bottles:

Castle lager lite, Black label, or Lion lager

Number of cans:

660 ml quartz

Number of bottles:

750 ml quarts

Number of bottles:

Other

What brand of beer?

Number of cans and/or bottles?

Wine

- 1000ml box
- 3000ml box
- 5000ml box
- Other (specify)

Number of 1000ml boxes:

Number of 3000ml boxes:

Number of 5000ml boxes:

What brand of wine?

How big were the boxes or bottles?

How many boxes or bottles?

Spirit coolers

- 275ml bottles
- Other (specify)

Number of 275ml bottles:

What brand of spirit cooler?

How big were the bottles or cans?

How many bottles or cans?

Hard liquor

- 200ml bottles
- 500ml bottles
- 750ml bottles
- 1000ml bottles
- Other (specify)

Number of 200ml bottles:

Number of 500ml bottles

Number of 750ml bottles:

Number of 1000ml bottles:

Liquor

What brand of liquor?

How big were the bottles?

Number of bottles?

DRUGS

1. Have you ever used marijuana or hashish?
   - Yes
   - No

How old were you the first time you used mariuana or hashish?

When was the last time you used marijuana or hashish?

How often do you use marijuana or hashish? (answer in days per week, days per month, or times in the past year)

Was there a period in the past when you used it more?

- Yes
- No

When was that?

How often did you use it at that time? (answer in days per week, days per month, or times in the past year)

2. Have you ever used tik?

- Yes
- No

How old were you the first time you used tik?

When was the last time you used tik?

How often do you use tik? (answer in days per week, days per month, or times in the past year)

Was the a period in the past when you used it more? Yes No

When was that?

How often did you use it at that time? (answer in days per week, days per month, or times in the past year)

Have you ever used any of the following:

A) Sniffing (glue, gas, paint, nail polish remover, propane, or any other solvent)?

- Yes
- No

How often do you use it?

B) Heroin (powder, smack, sugarbrown)?

- Yes
- No

How often do you use it?

C) Cocaine/crack (powder, smack, sugarbrown)?

- Yes
- No

How often do you use it?

D) Sedatives/tranquilizers (Valium, Librium, Xanax, Ativan)?

- Yes
- No

How often do you use it?

E) Antidepressants (Prozac, Paxil, Zoloft, Xipramol)?

- Yes

- No

How often do you use it?

F) Something else?

- Yes
- No

What is it?

How often do you use it?

4. Have you ever gone for help or treatment for drug abuse?

Yes

No

When was that? Where did you go? Detox?

Appendix H

BDI-II

Record ID:

ID:

Date:

Examiner:

This questionnaire consists of 21 groups of statements. Please read each group of statements carefully and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. If several statements in the group seem to apply equally well, choose the highest number for that group.

1. Sadness

    0. I do not feel sad.

    1. I feel sad much of the time.

    2. I am sad all the time.

    3. I am so sad or unhappy that I can't stand it.

2. Pessimism

    0. I am not discouraged about my future.

    1. I feel more discouraged about my future than I used to.

    2. I do not expect things to work out for me.

3. I feel my future is hopeless and will only get worse.

3. Past Failure

0. I do not feel like a failure.

1. I have failed more than I should have.

2. As I look back, I see a lot of failures.

3. I feel I am a total failure as a person.

4. Loss of Pleasure

0. I get as much pleasure as I ever did from the things I enjoy.

1. I don't enjoy things as much as I used to.

2. I get very little pleasure from the things I used to enjoy.

3. I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0. I don't feel particularly guilty.

1. I feel guilty over many things I have done or should have done.

2. I feel quite guilty most of the time.

3. I feel guilty all of the time.

6. Punishment Feelings

0. I don't feel I am being punished.

1. I feel I may be punished.

2. I expect to be punished.

3. I feel I am being punished.

7. Self-Dislike

0. I feel the same about myself as ever.

1. I have lost confidence in myself.

2. I am disappointed in myself.

3. I dislike myself.

8. Self-Criticalness

0. I don't criticize or blame myself more than usual.

1. I am more critical of myself than I used to be.

2. I criticize myself for all of my faults.

3. I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0. I don't have any thoughts of killing myself.

1. I have thoughts of killing myself, but I would not carry them out.

2. I would like to kill myself.

3. I would kill myself if I had the chance.

10. Crying

0. I don't cry anymore than I used to.

1. I cry more than I used to.

2. I cry over every little thing.

3. I feel like crying, but I can't.

11. Agitation

0. I am no more restless or wound up than usual.

1. I feel more restless or wound up than usual.

2. I am so restless or agitated, it's hard to stay still.

3. I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

    0. I have not lost interest in other people or activities.

    1. I am less interested in other people or things than before.

    2. I have lost most of my interest in other people or things.

    3. It's hard to get interested in anything.

13. Indecisiveness

    0. I make decisions about as well as ever.

    1. I find it more difficult to make decisions than usual.

    2. I have much greater difficulty in making decisions than I used to.

    3. I have trouble making any decisions.

14. Worthlessness

    0. I do not feel I am worthless.

    1. I don't consider myself as worthwhile and useful as I used to.

    2. I feel more worthless as compared to others.

    3. I feel utterly worthless.

15. Loss of Energy

    0. I have as much energy as ever.

    1. I have less energy than I used to have.

    2. I don't have enough energy to do very much.

    3. I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

    0. I have not experienced any change in my sleeping.

    1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0. I am not more irritable than usual.

1. I am more irritable than usual.

2. I am much more irritable than usual.

3. I am irritable all the time.

18. Changes in Appetite

0. I have not experienced any change in my appetite.

1a. My appetite is somewhat less than usual.

1b. My appetite is somewhat greater than usual.

2a. My appetite is much less than before.

2b. My appetite is much greater than usual.

3a. I have no appetite at all.

3b. I crave food all the time.

19. Concentration Difficulty

0. I can concentrate as well as ever.

1. I can't concentrate as well as usual.

2. It's hard to keep my mind on anything for very long.

3. I find I can't concentrate on anything.

20. Tiredness or Fatigue

    0. I am no more tired or fatigued than usual.

    1. I get more tired or fatigued more easily than usual.

    2. I am too tired or fatigued to do a lot of the things I used to do.

    3. I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

    0. I have not noticed any recent change in my interest in sex.

    1. I am less interested in sex than I used to be.

    2. I am much less interested in sex now.

    3. I have lost interest in sex completely.

Appendix I

BAI

Record ID:

ID:

Date:

Examiner:

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today.

1. Numbness or tingling

    0. I do not feel numbness or tingling

    1. I mildly feel numbness or tingling but it doesn't bother me much

    2. I moderately feel numbness or tingling and it wasn't pleasant

    3. I severely feel numbness or tingling and it bothered me a lot

2. Feeling Hot

    0. I do not experience feeling hot

    1. I mildly experience feeling hot but it doesn't bother me much

    2. I moderately experience feeling hot and it wasn't pleasant

    3. I severely experience feeling hot and it bothered me a lot

3. Wobbliness in Legs

0. I do not feel wobbliness in legs

1. I mildly experience wobbliness in legs but it doesn't bother me much

2. I moderately experience wobbliness in legs and it wasn't pleasant at times

3. I severely experience wobbliness in legs and it bothered me a lot

4. Unable to relax

0. I am able to relax

1. I am mildly unable to relax but it doesn't bother me much

2. I am moderately unable to relax and it wasn't pleasant at times

3. I am severely unable to relax and it bothered me a lot

5. Fear of worst happening

0. I do not have a fear of the worst happening

1. I mildly have a fear of the worst happening but it doesn't bother me much

2. I moderately have a fear of the worst and it is not pleasant at time

3. I severely have a fear of the worst and it bothers me a lot

6. Dizzy or lightheaded

0. I do not feel dizziness or lightheadedness

1. I mildly feel dizziness or lightheadedness but it doesn't bother me much

2. I moderately feel dizziness or lightheadedness and it doesn't feel pleasant at times

3. I severely feel dizziness or lightheadedness and it bothers me a lot

7. Heart Pounding/ Racing

0. I do not feel my heart pounding/racing

1. I mildly feel my heart pounding/racing but it doesn't bother me much

2. I moderately feel my heart pounding/racing and it doesn't feel pleasant at times

3. I severely feel my heart pounding/racing and it bothers me a lot

8. Unsteady

0. I do not feel unsteady

1. I mildly feel unsteady but it doesn't bother me much

2. I moderately unsteady and it doesn't feel pleasant at times

3. I severely feel unsteady and it bothers me a lot

9. Terrified or afraid

0. I do not feel terrified or afraid

1. I mildly feel terrified or afraid but it doesn't bother me much

2. I moderately feel terrified or afraid and it doesn't feel pleasant at times

3. I severely feel terrified or afraid and it bothers me a lot

10. Nervous

0. I do not feel nervous

1. I mildly feel nervous but it doesn't bother me much

2. I moderately feel nervous and it doesn't feel pleasant at times

3. I severely feel nervous and it bothers me a lot

11. Feeling of choking

0. I do not have a feeling of choking

1. I mildly have a feeling of choking but it doesn't bother me much

2. I moderately have a feeling of choking and it doesn't feel pleasant at times

3. I severely have a feeling of choking and it bothers me a lot

12. Hands trembling

0. I do not experience hands trembling

1. I mildly experience hands trembling but it doesn't bother me much

2. I moderately experience hands trembling and it doesn't feel pleasant at times

3. I severely experience hands trembling and it bothers me a lot

13. Shaky/unsteady

0. I do not feel shaky/unsteady

1. I mildly feel shaky/unsteady but it doesn't bother me much

2. I moderately feel shaky/unsteady and it doesn't feel pleasant at times

3. I severely feel shaky/unsteady and it bothers me a lot

14. Fear of losing control

0. I do not have a fear of losing control

1. I mildly have a fear of losing control but it doesn't bother me much

2. I moderately have a fear of losing control and it doesn't feel pleasant at times

3. I severely have a fear of losing control and it bothers me a lot

15. Difficulty breathing

0. I do not have difficulty in breathing

1. I mildly have difficulty in breathing but it doesn't bother me much

2. I moderately have difficulty in breathing and it doesn't feel pleasant at times

3. I severely have difficulty in breathing and it bothers me a lot

16. Fear of dying

0. I do not have a fear of dying

1. I mildly have a fear of dying but it doesn't bother me much

2. I moderately have a fear of dying and it doesn't feel pleasant at times

3. I severely have a fear of dying and it bothers me a lot

17. Scared

    0. I do not feel scared

    1. I mildly feel scared but it doesn't bother me much

    2. I moderately feel scared and it doesn't feel pleasant at times

    3. I severely feel scared and it bothers me a lot

18. Indigestion

    0. I do not experience indigestion

    1. I mildly experience indigestion but it doesn't bother me much

    2. I moderately experience indigestion and it doesn't feel pleasant at times

    3. I severely experience indigestion and it bothers me a lot

19. Faint/Lighthearted

    0. I do not feel faint/lightheaded

    1. I mildly feel faint/lightheaded but it doesn't bother me much

    2. I moderately feel faint/lightheaded and it doesn't feel pleasant at times

    3. I severely feel faint/lightheaded and it bothers me a lot

20. Face flushed

    0. I do not have face flushed

    1. I mildly have face flushed but it doesn't bother me much

    2. I moderately have face flushed and it doesn't feel pleasant at times

    3. I severely have face flushed and it bothers me a lot

21. Hot/cold sweats

    0. I do not have hot/cold sweats

    1. I mildly have hot/cold sweats but it doesn't bother me much

2. I moderately hot/cold sweats and it doesn’t feel pleasant at times

3. I severely have hot/cold sweats and it bothers me a lot

Appendix J

SSS

Record ID:

ID:

Examiner:

Date:

Time:

Stanford Sleepiness Scale "Alertness Test"

Pick which number best represents how you are feeling:

- Feeling active, vital, alert, or wide awake.
- Functioning at high levels, but not fully alert
- Awake, but relaxed; responsive but not fully alert
- Somewhat foggy, let down
- Foggy; losing interest in remaining awake; slowed down
- Sleepy, woozy, fighting sleep; prefer to lie down
- No longer fighting sleep, sleep onset soon; having dream-like thoughts
- Asleep

Appendix K

WRAML-II

Record ID:

ID:

Date:

Examiner:

WRAML WORD LIST IMMEDIATE

Say: “I will read you a long list of words. Try to remember as many of them as you can. Since it is a long list, you probably won’t remember all the words. Just do the best you can. It doesn’t matter in what order you repeat them.”

Read the list and then after each trial say: “Now tell me all the words you can remember.”

If no response: “How did the list begin?”

If they ask for help: “Just try your best, I’m not allowed to help you.”

Following Trial 1, say: “That was good. I am going to read the same list again. When I am finished, try to tell me even more words if you can. Tell me those words you have already said as well as any new ones you can remember. The order in which you repeat them does not matter.”

(4 TRIALS)

Say: "Ek gaan vir jou 'n lang lysie woorde lees. Probeer om soveel van die woorde te onthou soos wat jy kan. Omdat dit 'n lang lysie is, sal jy seker nie al die woorde onthou nie. Doen net jou beste. Dit maak nie saak in watter orde jy die woorde herhaal nie."

Read the list and then after each trial say: "Sê nou vir my al die woorde wat jy kan onthou."
If no response: "Hoe het die lysie begin?"
If they ask for help: "Probeer net jou beste, ek mag jou nie help nie."

Following Trial 1, say: "Ek gaan weer dieselfde lysie lees. Wanneer ek klaar is, probeer om vir my nog meer woorde te sê as jy kan. Sê vir my daardie wooorde wat jy alreeds gese het en ook enige nuwes wat jy kan onthou. Dit maak nie saak in watse volgorde jy hulle herhaal nie." (4 TRIALS)

Word List:

1. Sand/ sand
2. Game/ spiel
3. Hat/ hoed
4. Tree/ boom
5. Ear/ oor
6. Comb/ kam
7. Flag/ vlag
8. Wood/ hout
9. Map/ kaart

10. Door/ deur
11. Ice/ ys
12. Nail/ spyker
13. Boat/ boot
14. Page/ bladsy
15. Ant/ by
16. River/ rivier

Trial 1-4-- Record responses in box. Be sure to include words not on list.

WRAML STORIES DELAY

Do you remember the long list words that I read over and over again? Each time, I asked you to tell me the words that you could remember. Now, tell me as many words that you can remember as possible.

Onthou jy die lang lysie woorde wat ek oor en oor gelees het? Ek het jou elke keer gevra om die woorde vir my te sê wat jy kon onthou. Sê nou vir my soveel van die woorde as wat jy kan onthou.

Delayed Recall -- Record responses in box. Be sure to include words not on list.

WRAML STORIES IMMEDIATE

<u>Fishing Story</u>

Say: “I am going to read you a story. Listen carefully because when I am done, I will ask you to tell me as much of the story as you can remember.”

Then read the story with the speed and inflection appropriate to reading a story in an interesting manner to someone at the participant's developmental level.

"On Saturday, Annie was to go fishing for the first time. She was going with her mom. While putting on her shoes, Annie told her dad that she dreamed that she caught a giant fish that pulled her into the river. Dad thought that it was silly to worry, but suggested she take Oscar, their dog, along for protection. Besides, Oscar loved to go swimming.
Annie, Oscar and Mom walked to the lake only to find their old boat full of water from last night's rain. So instead of using the boat, Annie and Mom found a large rock to stand on so they wouldn't get their shoes wet. While Annie fished, Oscar slept under a shady bush.
After several hours passed and no one caught any fish, Mom turned away to make lunch. Just then, there was a big tug on her line. But when Mom grabbed for it, she slipped off the rock. Oscar jumped in to help. While Mom dried out, Annie reeled in the biggest catch of the day, a 5-kilogram trout."

Then say: "Now, tell me the story. Try to tell me all the parts."

If the participant is hesitant, the examiner may encourage by saying: "Just tell me the story in your own words." "Go ahead." "How did it begin?" or "What else to you remember?" or similar prompts.

Say: "Ek gaan vir jou 'n storie lees. Luister mooi. As ek klaar is, sal ek jou vra om vir my soveel van die storie te vertel as wat jy kan onthou."

Then read the story with the speed and inflection appropriate to reading a story in an interesting manner to someone at the participant's developmental level.

"Ansie sou Saturdag vir die eerste keer gaan visvang. Sy sou saam met haar ma gaan. Terwyl sy haar skoene aangetrek het, het Ansie vir haar pa vertel dat sy gedroom het dat sy 'n reuse vis gevang het wat haar in die dam ingetrek het. Pa het gedink dat dit sommer laf was om

bekommerd te wees, maar het voorgestel dat sy vir Oscar, hul hond, saamneem vir beskerming. Oscar was in elk geval baie lief daarvoor om te gaan swem.

Ansie, Oscar en Ma het dam toe gestap, maar vind toe daar hul ou boot vol water van die vorige aand se reën. In plaas daarvan om die boot te gebruik, het Ansie en Ma ‘n groot rots gevind om op te staan sodat hulle skoene nie nat word nie. Terwyl Ansie visgevang het, het Oscar onder die skaduwee van ‘n bos geslaap.

Na ‘n hele paar uur het niemand nog enige vis gevang nie, en Ma het weggedraai om middagete te maak. Op daardie oomblik was daar ‘n harde pluk aan haar lyn. Maar toe Ma daarna gryp, het sy van die rots af gegly. Oscar het ingespring om te help. Terwyl Ma haar afgedroog het, het Ansie die grootse vangs van die dag ingekatrol, ‘n 5-kilogram-karp.”

Then say: “Nou, vertel my die storie. Probeer my al die dele te vertel.”

If the participant is hesitant, the examiner may encourage by saying: “Vertel my die storie in jou eie woorde.” “Gaan voort.” “Hoe het dit begin?” or “Wat anders onthou jy?” or similar prompts.

Fishing Story Recall:

SATURDAY/ SATURDAG
- Yes
- No

(Item must be exact.)

Annie/ Ansie
- Yes
- No

Fishing/ visvang
- Yes
- No

first time/ eerste keer
- Yes
- No

Mom/ ma
- Yes
- No

put on shoes/ skoene aangetrek
- Yes
- No

told dad / vir haar pa gesê
- Yes
- No

Dreamed/ gedroom
- Yes
- No

giant fish/ reusevis
- Yes
- No

pulled her in/ ingetrek
- Yes
- No

dad thought it was silly to worry / Pa het gedink dat dit laf was om bekommerd te wees
- Yes
- No

OSCAR/ OSCAR
- Yes
- No

(Item must be exact.)

DOG/ HOND
- Yes
- No

(Item must be exact.)

Protection/ beskerming
- Yes
- No

loved swimming/ mal daaroor om te gaan swem
- Yes
- No

LAKE/ DAM
- Yes
- No

(Item must be exact.)

OLD/ OU
- Yes
- No

(Item must be exact.)

Boat/ boot
- Yes
- No

full of water/ vol water
- Yes
- No

last night/ gisteraand
- Yes
- No

RAIN/ REËN
- Yes
- No

(Item must be exact.)

Large/ groot
- Yes
- No

ROCK/ ROTS
- Yes
- No

(Item must be exact.)

shoes wet/ nat skoene
- Yes
- No

Oscar slept/ Oscar geslaap
- Yes
- No

SHADY/ SKADUWEE
- Yes
- No

(Item must be exact.)

BUSH/ BOS
- Yes
- No

(Item must be exact.)

several hours/ paar ure
- Yes
- No

no fish caught/ geen vis gevang nie
- Yes
- No

Lunch/ middagete
- Yes
- No

big tug/ groot pluk
- Yes
- No

mom slipped/ ma het afgegly
- Yes
- No

Oscar jumped in/ Oscar het ingespring
- Yes
- No

mom dried out/ ma afgedroog
- Yes
- No

Reeled/ ingekatrol
- Yes
- No

the biggest catch/ die grootste vangs
- Yes
- No

5-KILOGRAM/ VYF-KILOGRAM
- Yes
- No

(Item must be exact.)

TROUT/ KARP
- Yes
- No

(Item must be exact.)

Job Story:
After the participant completes the first story say: “That was fine. I will now read you one more story. Again, listen carefully so you can tell me as much of the story as possible.”

“It was the morning of February 1st, and it was to be one of the hottest days of the summer. It was also the day that Paul was to start his summer job at his dad’s store. Because Paul now had his driver’s license, his job was to deliver fruit and ice cream to the store before it opened at 6:30. His mom said that this was too much responsibility for a 17-year old but Paul wanted to prove her wrong.

Paul awoke at 5am and drove to the docks to get the bananas as they came off the boat. After loading them into the truck, Paul drove to the ice cream factory. There, Paul loaded 25 litres of chocolate and peach ice cream, and it was still early. The smell of the bakery next door reminded him that he had not eaten breakfast. In the middle of reading the paper, sipping coffee, and eating his third warm jelly donut, Paul realized that his dad’s store was to open in 15 minutes.

Paul’s father congratulated him when he arrived at the store with 2 minutes to spare. Paul was feeling proud until he noticed something creamy dripping from the back of the truck.”

Read the second story, say: “Now tell me this story. Try to tell me all the parts.”

If participant is hesitant, prompt in a similar manner as described above.

After participant completes the first story say: “Dit was goed. Ek gaan nou ‘n ander storie lees. Luister mooi, as ek klaar is, sal ek jou vra om vir my soveel van die storie te vertel as wat jy kan onthou.”

“Dit was die oggend van die eerste Februarie, en dit was een van die warmste dae van die somer. Dit was ook die dag waarop Paul se vakansiewerk by sy pa se winkel sou begin. Omdat Paul nou sy lisensie gehad het, was dit sy taak om vrugte en roomys by die winkel af te lewer voordat dit om half sewe oopmaak. Sy ma het gesê dat dit te veel verantwoordelikheid vir ‘n sewentien-jarige was, maar Paul wou haar verkeerd bewys.

Paul het om 5-uur wakker geword en na die hawe toe gery om die piesangs te kry wat van die boot afkom. Nadat hy hulle in die bakkie gelaai het, het Paul na die roomysfabriek toe gery. Daar het Paul vyf-en-twintig liter sjokolade-en perskeroomys opgelaai, en dit was nog vroeg. Die reuk van die bakkery langsaan het hom daaraan herinner dat hy nog nie ontbyt geëet het nie. Terwyl hy die koerant gelees, koffie gedrink en sy derde warm mosbolletjie geëet het, het Paul besef dat sy pa se winkel oor vyftien minute gaan oopmaak.

Paul se pa het hom gelukgewens toe hy 2 minute vroeg by die winkel aankom. Paul het trots gevoel, totdat hy opgemerk het dat iets romerig van die agterkant van die bakkie af drup.”

Read the second story, then say: “Nou, vertel my die storie. Probeer my al die dele te vertel.”

If participant is hesitant, prompt in a similar manner as described above.

Job Story Recall

MORNING/ OGGEND
- Yes
- No

(Item must be exact.)

FEBRUARY 1ST/ EEN FEBRUARIE
- Yes
- No

(Item must be exact.)

one of the hottest days/ een van die warmste dae
- Yes
- No

Paul/ Paul
- Yes
- No

start job/ begin werk
- Yes
- No

dad's store/ pa se winkel
- Yes
- No

LICENSE/ LISENSIE
- Yes
- No

(Item must be exact.)

delivery job/ aflewering werk
- Yes
- No

FRUIT/ VRUGTE
- Yes
- No

(Item must be exact.)

ICE CREAM/ ROOMYS
- Yes
- No

(Item must be exact.)

before store opened/ voor die winkel opmaak
- Yes
- No

mom said/ ma het gesê
- Yes
- No

too much responsibility/ te veel verantwoordelikheid
- Yes
- No

SEVENTEEN/ SEWENTIEN
- Yes
- No

(Item must be exact.)

prove her wrong/ wou haar verkeerd bewys
- Yes
- No

Awoke/ Wakker geword
- Yes
- No

FIVE/ VYF
- Yes
- No

(Item must be exact.)

Docks/ hawe
- Yes
- No

BANANAS/ PIESANGS
- Yes
- No

(Item must be exact.)

came off the boat/ van die boot afgekom het
- Yes
- No

truck loaded/ bakkie gelaai het
- Yes
- No

FACTORY/ FABRIEK
- Yes
- No

(Item must be exact.)

25 LITRES/ 25 LITER
- Yes
- No

(Item must be exact.)

CHOCOLATE/ SJOKOLADE
- Yes
- No

(Item must be exact.)

PEACH/ PERSKE
- Yes
- No

(Item must be exact.)

ICE CREAM/ ROOMYS
- Yes
- No

(Item must be exact.)

Smell/ reuk
- Yes
- No

BAKERY/ BAKKERY
- Yes
- No

(Item must be exact.)

next door/ langsaan
- Yes
- No

not eaten breakfast/ nie ontbyt geëet het nie
- Yes
- No

COFFEE/ KOFFIE
- Yes
- No

(Item must be exact.)

THIRD DONUT/ DERDE MOSBOLLETJIE
- Yes
- No

(Item must be exact.)

store to open/ winkel oopmaak
- Yes
- No

FIFTEEN MINUTES/ VYFTIEN MINUUTE
- Yes
- No

(Item must be exact.)

father congratulated/ pa het home gelukgewens
- Yes
- No

TWO MINUTES/ TWEE MINUUTE
- Yes
- No

(Item must be exact.)

to spare/ vroeg
- Yes
- No

feeling proud/ Trots gevoel
- Yes
- No

noticed dripping/ iets wat drup
- Yes
- No

back of truck/ agterkant van die bakkie
- Yes
- No

WRAML STORIES DELAY

A little while ago I read you a Fishing Story. Try to tell it to me again remembering as many parts as you can.

Ek het ‘n rukkie terug vir jou ‘n Visvangstorie gelees. Probeer dit weer vir my vertel en onthou soveel van dit as wat jy kan.”

Now I want you to tell me again the Summer Job Story. Tell me as many parts you can now remember.

Nou wil ek hê dat jy weer vir my die Somerwerk-storie vertel. Vertel my soveel van dit as wat jy kan onthou.

Appendix L

Consent Forms

Research Informed Consent

Title of Study: Contribution of Sleep Disruption to Memory Impairment and Emotion Dysregulation in Fetal Alcohol Spectrum Disorders

We would like to invite you to continue to take part in our research study that you have been part of since you were born. Please read this form and ask us any questions you may have before agreeing to be in the study. This study is being conducted by Kevin Thomas, Ph.D., and Gosia Lipinska, Ph.D., from the Psychology Department, and Ernesta Meintjes, Ph.D., from the Faculty of Health Sciences of the University of Cape Town, and Sandra W. Jacobson, Ph.D., and Joseph L. Jacobson, Ph.D., from Wayne State University in the United States. It is being supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the United States. The study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, as well as South African research ethics guidelines, as documented by the Department of Health in "Ethics in health research: principles, processes and structure" (2nd Edition, 2015).

Study Purpose: The purpose of this study is to see how sleep affects learning and memory and emotions and to better understand how smoking and drinking alcohol during pregnancy can affect what happens to memories and emotions during sleep. We are inviting the participants who were in our University of Cape Town Mother-Child Developmental Study cohort to come back again.

If you agree to take part in this study, we will give you a cell phone and call you each morning for 7 days in a row. During each call, we will ask you questions about how you slept the night before and how you are feeling at that moment. After that week of phone calls is over, we will make appointments for you to come to our Sleep Sciences Laboratory at the University of Cape Town for 3 nights in a row. On the day of each appointment, one of our research team will drive you to the Laboratory so that you get there at

about 7 pm. When you arrive there, a research assistant will give you instructions for what you will do before going to sleep. On each night, you will be given a light meal. We will ask you to give us a urine sample. These urine samples will only be labeled with your study ID number. Then you will fill out some questionnaires, do some memory tests, or look at some pictures and tell us how you feel about them. These things will take about 2 hours. Before going to sleep, the research assistant will attach some wires and electrodes to you so that we can monitor your sleep. Each night, you will go to sleep at about 10 pm. Each morning, you will wake up at about 8 am and then complete some more tasks and questionnaires. These will take about 1 hour. After you have done that and eaten a light breakfast, a member of the research team will drive you home.

Benefits: There may be no direct benefits for you; however, information from this study may benefit other people now or in the future. If a serious problem is found, we will tell you and refer you to a doctor and/or someone who can help, if you would like us to do so. If you are suffering from any major illness, we will send you to Groote Schuur Hospital. No information about you will be given to any doctors, hospitals, or schools unless you ask us and allow us to do so in writing.

Risks: There are only minimal risks to you. Specifically, in one of the tests we give you may see some pictures that are upsetting. Before you leave the Laboratory, we will discuss those pictures and your reaction to them, and if you are still upset we will make sure that a counselor is available to you.

What if Something Goes Wrong? The University of Cape Town undertakes that in the event that you suffer any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity, that is caused by your participation in the study, it will provide immediate medical care. The University of Cape Town has appropriate insurance cover to provide prompt payment of compensation for any research-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (University of Cape Town), without legal commitment, should compensate you without you having to prove that University of Cape Town is at fault. An injury is considered research-related if, and

to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the research study, whether they are research-related or other related complications. If you think that you have suffered a research-related injury, please contact Dr. Kevin Thomas right away at 021-650-4608 (Department of Psychology, Rondebosch 7701, PD Hahn Building, Room 2.17, Cape Town). The University of Cape Town reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request. No reimbursement, compensation, or free medical care is offered by Wayne State University.

Study Costs: There will be no cost to you for taking part in this research study.

Compensation: For taking part in this research study, we will pay you R250 for each visit, which comes to a total of R750 for the three visits; dinner each sleep night; and breakfast each sleep morning. We will also give you a cell phone, which you will be allowed to keep after the study, plus R100 airtime.

Confidentiality: We will keep all information collected about you during the study secret to the extent permitted by law. You will be identified in the research records by a code number. We will not give out information that names you unless you give us written permission, but your records may be reviewed by the study sponsor (NIAAA), the Human Investigation Committee at Wayne State University, or governmental agencies with appropriate regulatory oversight (e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), Office of Civil Rights (OCR), etc.). Access to your name is limited to project staff members who need to contact you by telephone or in person. Information from this study and photos may be presented in scientific meetings or journals, but your identity will be kept confidential, and your name will not be used.

Voluntary Participation/Withdrawal: You do not have to take part in this study. You may decide to take part and later change your mind and stop taking part. You are also free not to answer any questions or to

stop before the procedure is finished. The researcher or the sponsor may stop your taking part in this study without your agreement. Your decisions will not change any present or future relationship with the medical center or other services you are entitled to receive.

Questions: If you have any questions now or in the future, you may contact Dr. Kevin Thomas at 021-650-4608 or Dr. Sandra W. Jacobson at 001-313-993-5454. If you have questions or concerns about your rights as a research participant, you can contact the Chair of the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (021-406-6338) or the Chair of the Wayne State University Human Investigation Committee (001- 313-577-1628).

Consent to Participate in a Research Study: To voluntarily agree to take part in this study, you must sign on the line below. If you decide to take part, you may quit at any time. You are not giving up any of your legal rights by signing this form. Your signature shows that you have read, or had read to you, this entire consent form, including the risks and benefits, and that we have answered all your questions. We will give you a copy of this consent form to take home.

_____	_____
Signature of Participant	Date
_____	_____
Printed Name of Participant	Time
_____	_____
Signature of Parent/Guardian (When applicable)	Date
_____	_____
Printed Name of Parent/Guardian (When applicable)	Time
_____	_____

*Signature of Witness (When applicable) Date

_____ _____

Printed Name of Witness Time

_____ _____

Signature of Person Obtaining Consent Date

_____ _____

Printed Name of Person Obtaining Consent Time

*Use when participant has had consent form read to them (i.e., illiterate, legally blind, translated into foreign language).

Ingeligte Toestemming tot Navorsing

Titel van Studie: Bydrae van Slaapstoornis tot Geheueverswakking en Emosie-dysregulering in Fetale Alkoholspektrumafwykings

Ons wil u graag uitnooi om verder deel te neem aan ons navorsingstudie waaraan u al deelneem sedert u geboorte. Lees asseblief hierdie vorm deur en vra ons enige vrae wat u mag hê voordat u instem om aan die studie deel te neem. Hierdie studie word uitgevoer deur Kevin Thomas, Ph.D., en Gosia Lipinska, Ph.D., van die Departement Sielkunde, en Ernesta Meintjes, Ph.D., van die Fakulteit Gesondheidswetenskappe aan die Universiteit van Kaapstad, en Sandra W. Jacobson, Ph.D., en Joseph L. Jacobson, Ph.D., van Wayne Staatsuniversiteit in die Verenigde State. Dit word ondersteun deur die Nasionale Instituut vir Alkohol Misbruik en Alkoholisme (NIAAA) in die Verenigde State. Die studie sal uitgevoer word volgens die etiese riglyne en beginsels van die internasionale Verklaring van Helsinki, asook die Suid-Afrikaanse navorsings etiek riglyne soos weergegee deur die Departement van Gesondheid in “Etiek in gesondheids navorsing: beginsels, prosesse en strukture” (2de Uitgawe, 2015).

Doel van die Studie: Die doel van hierdie studie is om te sien hoe slaap 'n mens se leervermoë en geheue en emosies beïnvloed, en om beter te verstaan hoe rook en die drink van alkohol tydens swangerskap 'n invloed kan hê op wat met herinneringe en emosies tydens slaap gebeur. Ons nooi die 90 deelnemers wat in ons Universiteit van Kaapstad Moeder-Kind Ontwikkelingstudie groep was om weer terug te kom.

Ons wil graag hê dat u vir drie nagte agter mekaar na ons slaapsentrum toe moet kom en daar slaap. Elke aand wat u daar is, sal u 'n paar vraelyste invul, geheue toetse doen, of na 'n paar foto's kyk en ons vertel hoe u daaroor voel. Hierdie dinge sal ongeveer 2 ure duur in die aand voordat u gaan slaap, en dan ongeveer 1 uur in die oggend nadat u wakker geword het. Geen inligting oor u sal vir mediese of opvoedkundige doeleindes uitgedeel word nie, tensy ons u skriftelik vra.

Indien u instem om aan hierdie studie deel te neem, sal ons vir u 'n selfoon gee en u elke oggend bel vir 7 dae in 'n ry. Tydens elke oproep, sal ons vir u vrae vra oor hoe u die vorige aand geslaap het en hoe u op

daardie oomblik voel. Nadat daardie week van telefoonoproepe verby is, sal ons vir u afsprake maak om vir 3 nagte in 'n ry na ons Slaapwetenskaplaboratorium aan die Universiteit van Kaapstad te kom. Op die dag van elke afspraak sal 'n lid van ons navorsingspan u na die Laboratorium vervoer sodat u om ongeveer 7 nm daar sal aankom. Wanneer u daar aankom, sal 'n navorsingsassistent vir u instruksies gee oor wat u sal doen voordat u gaan slaap. U sal elke aand 'n ligte ete ontvang. Ons sal u vra om vir ons 'n urinemonster te gee. Hierdie urienmonsters sal slegs met u studie-ID-nommer gemerk word. Dan sal u 'n paar vraelyste invul en 'n paar leer- en geheuetake voltooi. Voordat u gaan slaap, sal die navorsingsassistent 'n paar drade en elektrodes aan u vasheg sodat ons u slaap kan monitor. U sal elke aand omtrent 10 nm gaan slaap. U sal elke oggend omtrent 8 vm wakker word en dan nog 'n paar take doen en vraelyste invul. Nadat u dit gedoen het en 'n ligte ontbyt geëet het, sal 'n lid van die navorsingspan u weer huis toe neem.

Voordele: Daar mag dalksal geen direkte voordele vir u wees nie, maar inligting van hierdie studie kan tot die voordeel van ander mense wees, nou of in die toekoms. Indien ‘n ernstige probleem gevind word, sal ons vir u sê en u verwys na ‘n dokter en/of iemand wat kan help, indien u wil hê ons moet dit doen. Indien u aan enige ernstige siekte ly, sal ons u na Groote Schuur Hospitaal stuur. Geen inligting oor u sal aan enige dokters, hospitale, of skole gegee word nie tensy u ons vra om dit te doen en ons skriftelik toelaat.

Risiko’s: Daar is geen bekende risiko’s aan u nie.

Wat as Iets Verkeerd Gaan?

Die Universiteit van Kaapstad (UK) onderneem dat indien u enige noemenswaardige agteruitgang in gesondheid of welstand ondervind, of ly aan enige onverwagte sensitiwiteit of newe effek, wat veroorsaak is deur u deelname aan die studie, UK onmiddelike mediese sorg sal voorsien. UK het die toepaslike versekering om vinnig vergoeding te betaal vir enige navorsingsverwante besering volgens die riglyne van die “Association of the British Pharmaceutical Industry”, ABPI 1991. Basies beveel die ABPI riglyne aan dat die versekerde besigheid (UK), sonder wederregterlike voorbehoud, u moet vergoed sonder dat u

hoef te bewys dat dit UK se fout of skuld was. ‘n Besering word beskou as navorsingsverwant indien, en tot die mate wat, dit veroorsaak is deur die aktiwiteite van die studie. U moet die studie doktor onmiddelik in kennis stel van enige newe effek en/of besering gedurende die studie, nieteenstaande of dit navorsingsverwant is of aan ‘n ander komplikasie verwant is nie. Indien u dink dat u 'n navorsingsverwante besering opgedoen het, kontak asseblief Dr. Kevin Thomas dadelik by 021-650-4608 (Departement Sielkunde, Rondebosch 7701, PD Hahn-gebou, Kamer 2.17, Kaapstad).

UK behou die reg om nie vergoeding te voorsien nie as, en tot die mate wat, u besering te weeg gebring is omdat u gekies het om nie die instruksies wat u gegee is terwyl u deelgeneem het aan die studie te volg nie. U wettiglike reg om vergoeding te vereis vir ‘n besering waar u nalatigheid bewys word nie hierdeur beïnvloed nie. Afskrifte van hierdie riglyne is beskikbaar indien u dit versoek. Geen terugbetaling, vergoeding, of gratis mediese sorg word deur Wayne Staatsuniversiteit verskaf nie.

Studiekoste: U hoef niks te betaal om deel te neem aan hierdie studie nie.

Compensation: Vir u deelname aan hierdie navorsingstudie sal ons u R250 betaal vir elke besoek, wat altesaam R750 vir die drie besoeke beloop; ons sal vir u 'n selfoon gee plus R100 lugtyd; aandete elke slaapnag; en ontbyt elke slaapoggend.

Vertroulikheid: Ons sal alle inligting wat ons oor u versamel het tydens hierdie studie geheim hou, tot die mate wat die wet dit toelaat. As daar egter op enige stadium tydens die assessering inligting oor 'n bedreiging of gevaar vir u of ander geopenbaar word, moet ons daardie inligting onmiddellik rapporteer, voordat u die laboratorium verlaat, sodat ons hulp vir u kan verkry en 'n verwysing gerig kan word na toepaslike dienste. In die studie sal uU sal in die navorsingsrekords deur 'n kodenommer geïdentifiseer word. Ons sal geen inligting wat u by naam bekend maak uitgee nie tensy u vir ons skriftelike toestemming gee. U rekords mag egter hersien word deur die borg van die studie (NIAAA), die Menslike Navorsingskomitee by Wayne Staatsuniversiteit, of ander regeringsliggame (bv. Voedsel- en Dwelmmiddel-administrasie (FDA), Kantoor vir Menslike Navorsingsbeskerming (OHRP), Kantoor van

Burgerlike Regte (OCR), ens). Toegang tot u naam is beperk tot die projekpersoneellede wat dit benodig om u per telefoon of in persoon te kontak. Inligting en foto's van hierdie studie mag aangebied word in wetenskaplike vergaderings of joernale, maar u identiteit sal geheim gehou word en u naam sal nie gebruik word nie.

Vrywillige Deelname/Onttrekking: U hoef nie aan hierdie studie deel te neem nie. U kan kies om deel te neem aan die studie en later van besluit verander en ophou deelneem. U het ook die reg om 'n vraag nie te antwoord nie of om enige taak of onderhoud te stop voordat dit klaar is. Die navorser, of die borg, mag u deelname aan hierdie studie stop selfs al stem u nie daarmee saam nie. U besluite sal nie enige huidige of toekomstige verhouding tussen u en die mediese sentrum of ander dienste waartoe u geregtig is, affekteer nie.

Vrae: Indien u nou of op 'n latere stadium enige vrae het kan u Dr. Kevin Thomas skakel by 021- 650-4608 of Dr. Sandra W. Jacobson by 001-313-993-5454. Indien u enige vrae het of bekommerd is oor u regte as 'n deelnemer aan die studie, kan u die Voorsitter van die Menslike Navorsingsetiek Komitee van die Fakulteit van Gesondheidswetenskappe by die Universiteit van Kaapstad kontak (021-406-6338) of die Voorsitter van die Wayne Staatsuniversiteit se Menslike Ondersoek Komitee (001-313-577-1628) skakel.

Toestemming om aan die Navorsingsstudie Deel te Neem: Om vrywilliglik in te stem om aan hierdie studie deel te neem, moet u hieronder teken. Indien u kies om deel te neem, mag u op enige stadium u deelname stop. U gee nie enige van u regte op deur hierdie vorm te teken nie. U handtekening wys dat u hierdie vorm heeltemal deurgelees het, of dat dit aan u voorgelees is, insluitende die dele wat die risiko's en voordele verduidelik, en dat ons al u vrae beantwoord het. Ons sal vir u 'n afskrif van hierdie toestemmingsvorm gee om huis toe te vat.

_____ _____

Handtekening van Deelnemer Datum

_____ _____

Naam van Deelnemer in Drukskrif Tyd

_____ _____

Handtekening van Ouer/voog (Wanneer van toepassing) Datum

_____ _____

Naam van Ouer/Voog in Drukskrif Tyd

_____ _____

*Handtekening van Getuie (Wanneer van toepassing) Datum

_____ _____

Naam van Getuie in Drukskrif Tyd

_____ _____

Handtekening van Persoon wat Toestemming Ontvang Datum

_____ _____

Naam van Persoon wat Toestemming Ontvang in Drukskrif Tyd

*Gebruik wanneer die toestemmingvorm aan die deelnemer voorgelees is (dit is, in gevalle van ongeletterdheid, blindheid, vertaling in ’n ander taal).

Appendix M

Supplementary Table 1

Correlations Between Sample Characteristics, Dose-related PAE and Memory Retention (N = 76)

Variable	AA/dd	Story Task	Word List Task
Age	-.28 (.011)*	-.02 (.819)	-.16 (.164)
SES	-.35 (.001)**	.36 (.001)**	.00 (.963)
BDI-II	.07 (.513)	-.21 (.059)	-.20 (.075)
BAI	-.04 (.677)	.05 (.657)	-.26 (.018)*
ICV	.07 (.551)	-.24 (.036)*	-.25 (.028)*
SSS_{Night}	.25 (.028)*	.09 (.412)	.12 (.300)
$SSS_{Morning}$	.00 (.957)	.10 (.384)	.12 (.295)
Marijuana	.14 (.200)	.02 (.846)	-.17 (.139)
Cigarettes	.13 (.249)	-.24 (.039)*	-.06 (.591)
Tik	.20 (.079)	-.00 (.945)	.11 (.312)
Tranquilisers	.03 (.742)	.09 (.435)	-.05 (.647)
DD Week	.04 (.684)	.18 (.113)	-.01 (.895)
DD Two Week	-.02 (.844)	.08 (.452)	-.13 (.262)
DD Month	.00 (.956)	.04 (.718)	-.10 (.389)
AA Week	.05 (.656)	.13 (.244)	-.02 (.833)
AA Two Week	.03 (.743)	.06 (.604)	-.14 (.215)
AA Month	.05 (.623)	-.01 (.888)	-.13 (.268)
PSQI Global	.02 (.803)	.05 (.644)	-.07 (.542)
Ave SQ Pre	-.23 (.043)*	-.00 (.995)	-.19 (.092)
Ave SE Pre	-.11 (.313)	.02 (.832)	-.12 (.277)

Note. Spearman and Pearson correlations reported with p-values in parentheses. AA/dd = Absolute alcohol consumed per drinking day; SES = Socio-economic status (determined through Hollingshead Index); BDI-II = Beck Depression Inventory second edition; BAI = Beck Anxiety Inventory; ICV =

Intracranial volume; SSS = Standford Sleepiness Scale; DD Week = Drinking days over the past week; DD Two Week = Drinking days over the past two weeks; DD Month = Drinking days over the past month; AA Week = Units of absolute alcohol consumed over the past week; AA Two Week = Units of absolute alcohol consumed over the past two weeks; AA Month = Units of absolute alcohol consumed over the past month; PSQI Global = Pittsburgh Sleep Quality Index global score; SQ = Sleep Quality; SE = Sleep efficiency. $^{*}p < .05$. $^{**}p < .01$.

Appendix N

Supplementary Table 2

Correlations Between Memory Retention and SWS Macro- and Micro-architecture (N = 76)

Variable	Story Task	Word List Task
SWS min	.16 (.150)	.24 (.032*)
SWS %	.14 (.144)	.23 (.039*)
SWS Arousals	.01 (.960)	-.15 (.196)
SWS Arousals LOS	0.08 (.446)	--.23 (.038*)
SO PSD	.13 (.232)	-.03 (.769)
Delta PSD	-.02 (.821)	-.03 (.797)
SWA PSD	-.01 (.910)	-.02 (.825)
Density	.12 (.320)	-.03 (.794)
Amplitude	.17 (.124)	.18 (114)
Duration	-.34 (.002**)	-.16 (.149)
Frequency	.13 (.256)	.13 (.233)
Sigma Power	.16 (.165)	.16 (.150)
Fast CP %	.24 (.034*)	.16 (.151)
Fast CP Phase	-.30 (.007**)	-.07 (.529)
Fast CP Strength	-.24 (.031*)	-.14 (.202)

Note. Spearman and Pearson correlations reported with p-values in parentheses. SWS =Slow-wave sleep; LOS = Lightening of sleep; SO = Slow oscillation; PSD = Power spectral density; SWA = Slow-wave activity; CP = Coupling. $^{*}p < .05$. $^{**}p < .01$.

Appendix O

Supplementary Table 3

Linear Regression Models: Predicting Retention of Neutral Declarative Information, through a Story Task, over a sleep-filled delay using FASD Diagnostic Group, Childhood Hippocampal Volume, SWS Micro-architecture and Covariates (N = 76)

	Estimate	*SE*	*p*	*ESE*
Variable				
Intercept[a]	149.30	35.61	< .001***	
FASD Group				.11
FASD HE vs HC	-15.89	6.64	.019*	.67
FASD FAS/PFAS vs HC	-8.28	7.19	.253	.35
Fast Spindle Duration	-113.07	42.87	.010*	.14
SES	0.96	0.40	.018*	.08
Intercept[b]	270.60	72.42	< .001***	
FASD Group				.13
FASD HE vs HC	-9.42	6.73	.166	.42
FASD FAS/PFAS vs HC	-15.03	7.72	.056	.67
Fast CP Strength	-746.80	297.10	.014*	.11
Left HV	-0.03	0.01	.027*	.00
SES	1.19	0.40	.004**	.16
ICV	-4.721e-05	1.984e-05	.020*	.06
Fast CP Strength x Left HV	0.01	0.08	.023*	.08
Intercept[c]	60.21	12.88	< .001***	
FASD Group				.12
FASD HE vs HC	-13.15	6.78	.056	.56
FASD FAS/PFAS vs HC	-11.97	7.27	.104	.50

Fast CP %	0.88	0.40	.030*	.08
SES	0.83	0.41	.048*	.09
Sex Male vs Female	-11.69	5.83	.049*	.05

Note. Supplementary models. FASD = Fetal alcohol spectrum disorder; HE = Heavily exposed; HC = Healthy controls; FAS/PFAS = fetal and partial fetal alcohol syndrome; SES = Socio-economic status; CP = Coupling; HV = Hippocampal Volume; ICV = Intracranial volume. [a] Fast Spindle Duration: Adjusted R^2 = 22.80%, F (4, 70) = 6.464, $p < .001$; [b] Fast Spindle Coupling Strength: Adjusted R^2 = 30.94%, F (7, 63) = 5.480, $p < .001$; [c] Fast Spindle Coupling Percentage: Adjusted R^2 = 22.28%, F (5, 69) = 5.242, $p < .001$. ESE = Effect size estimate: Eta^2 was used for all variables except individual FASD group contrasts for which standardised mean difference was calculated. *$p < .05$. **$p < .01$. ***$p < .001$.

Appendix P

Supplementary Table 4

Linear Regression Models: Predicting Retention of Neutral Declarative Information, through a Word-list Task, over a Sleep-filled Delay using FASD Diagnostic Group, Childhood Hippocampal Volume, SWS Macro-architecture and Covariates (N = 76)

	Estimate	*SE*	*p*	*ESE*
Intercept[a]	78.05	15.59	<.001***	
FASD Group				.00
FASD HE vs HC	30.10	13.50	.029*	.20
FASD FAS/PFAS vs HC	12.94	13.58	.343	.13
SWS min	0.34	0.11	.003**	.10
Ave SQ Pre	-6.78	2.89	.022*	.05
BAI	-0.58	0.19	.003**	.13
SWS min x FASD Group				.09
SWS min x HE vs HC	-0.43	0.16	.011*	.02
SWS min x FAS/PFAS vs HC	-0.19	0.15	.219	.01
Intercept[b]	68.49	52.3	.194	
LOS SWS	15.57	9.74	.114	.04
Left HV	0.01	0.01	.308	.02
ICV	-3.142e-05	1.603e-05	.054	.06
LOS SWS x Left HV	-4.412e-03	2.562e-03	.089	.04

Note. Supplementary models. FASD = Fetal alcohol spectrum disorder; HE = Heavily exposed; HC = Healthy controls; FAS/PFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; SWS = Slow-wave sleep; SQ = Sleep quality; BAI = Beck anxiety inventory; LOS = Lightening of sleep; HV = Hippocampal volume; ICV = Intracranial volume. [a] SWS minutes: Adjusted R^2 = 21.95%, F (7, 66) = 3.933, p = .001; [b] LOS SWS: Adjusted R^2 = 9.51%, F (4, 66) = 2.841, p = .030. ESE = Effect size estimate: Eta^2 all variables except for individual FASD group contrasts for which standardised mean difference

was calculated and individual FASD group interactions for which residual standard deviation was used. *$p < .05$. **$p < .01$. ***$p < .001$.