Exposure to Air Pollution Affects Performance on Hippocampus-Dependent Cognitive Tasks

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Contents

Abstract

The effects of exposure to air pollution on cardiovascular and pulmonary health are well explored in current literature. However, an understanding of how such pollutants may affect cognitive function is yet to be reached. This paper first reviews the available literature assessing the link between both acute and chronic exposure to air pollution – specifically to particulate matter (PM) and nitrogen dioxide (NO_2) – and cognitive function. The results from this review suggest that investigation of the effects of AP on hippocampus-based functions, including spatial navigation and memory, would also be beneficial This paper then describes the methodology employed in a pilot study to address the link between lifetime exposure to PM2.5 and NO_2 and performance on hippocampus-dependent tasks. 46 participants (12 males; 20.73 [*SD* = 3.68]), recruited at the University of Birmingham, completed 3 cognitive tasks: a hippocampus-dependent spatial working memory task (MemoryArena), a hippocampus-dependent transfer learning task (TL) and a hippocampus-independent attention network task (ANT). Lifetime Exposure to PM2.5 was significantly positively correlated with the number of training trials required to reach 80% accuracy on the MemoryArena task; participants who had been exposed to higher levels of PM2.5 throughout their lifetime required more (XX trials/ppb PM2.5 exposure) training trials to learn the correct configuration of items. Performance on the Phase 1 of the TL task – which corresponds to acquiring knowledge of the initial associations between items – was correlated with lifetime exposure to PM2.5 (r = .392*, p = .010), lifetime exposure to NOx (r = .372*, p = .015) and exposure to NOx in the last 3 years (r = .359*, p = .020). In the ANT, exposure to PM2.5 and NO_2 was also linked with increased reaction time (secs) on Congruent Valid trials (r = .552**, p = .000[b]; and r = .500**, p = .002 respectively). Exposure to PM2.5 since moving to Birmingham was significantly associated with Reaction Time (secs) on Incongruent Valid trials (r = .337*, p = .045) and Incongruent Invalid trials (r = .340*, p = .043). Implications of these finding and proposed future directions are discussed.

This project will explore the relationship between cognitive function and both acute and chronic exposure to air pollution. Throughout this report, reference will be made to themes which cross the disciplines of cognitive psychology and atmospheric chemistry. It will be assumed that the reader of this report does not possess expertise in either field and therefore appropriate explanation of all relevant concepts will be provided.

(1) Introduction

(1.1) An Introduction to Cognition

Cognition is defined as 'the mental action or process of acquiring knowledge and understanding through thought, experience and the senses' (Oxford English Dictionary, Simpson & Weiner, 1989) and encompasses faculties such as attention, memory, reasoning, problem solving, decision making and language production. Research within the field of cognitive psychology focusses on understanding these psychological functions as a function of neurological, environmental and biological factors. Indeed, despite evidence which suggests cognition is approximately 50% to 70% heritable (Bouchard & McGue, 1981), research has shown other factors such as neurological damage and environmental stressors to have a profound influence on many cognitive faculties. For example, in patients with Alzheimer's Disease, a degradation in memory ability is thought to be a downstream effect of neurological damage (Mecocci, MacGarvey & Beal, 1994). Furthermore, environmental factors such as parental stimulation and socioeconomic status have been shown to predict greater academic achievement in school children (Lugo-Gil & Tamis-LeMonda, 2008). The field of cognitive psychology conducts research which aims to understand the complex interaction between internal and external factors on cognitive function.

A number of brain regions will be referenced in this report; a diagram illustrating the major areas referred to is presented below (Figure 1). Please note that for deep brain structures including the hippocampus, see Figure 2 in section 1.7.2.

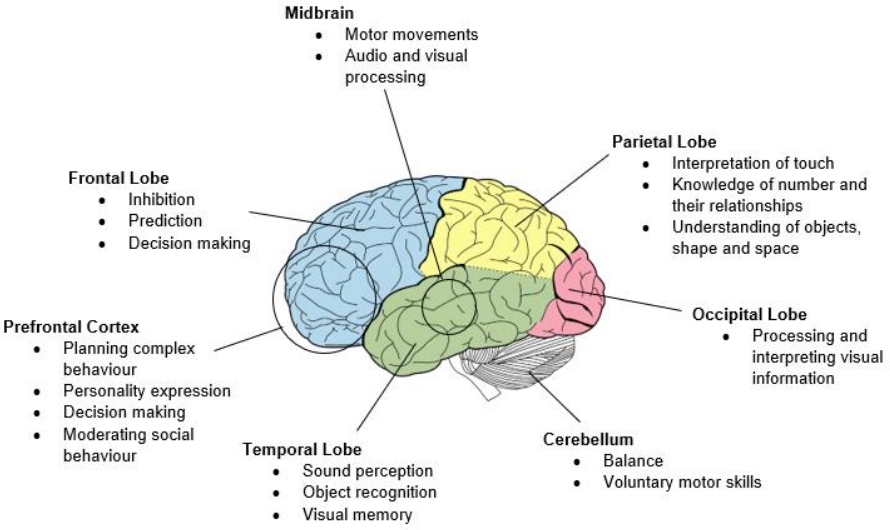

Figure 1. Major brain areas referred to in this report and their broad functions. Adapted from https://en.wikipedia.org/wiki/Cerebrum

(2) An Introduction to Air Pollution

Air pollutants (AP) can be defined as 'any substance emitted into the air from an anthropogenic, biogenic, or geogenic source, that is either not part of the natural atmosphere or is present in higher concentrations than in the natural atmosphere, and may cause a short-term or long-term adverse effect' (Daly & Zannetti, 2007; p.3). The Department for Environment, Food and Rural Affairs (DEFRA) lists the principal pollutants produced by industrial, domestic and traffic sources to be: sulphur dioxide, nitrogen oxides (NO_x), particular matter (measured as, for example, PM10, PM2.5 or PM1), ozone (O_3) and volatile organic compounds (VOCs), Toxic Organic Micro-Pollutants (TOMPS), benzene, 1,3-Butadiene, carbon monoxide (CO), lead (Pb) and heavy metals (DEFRA, 2011). These compounds can be emitted directly into the atmosphere by a range of human activities, including high temperature combustion (in vehicles and industry), metal processing and the burning of fossil fuels. Particulate matter (PM) and O_3 can also be produced indirectly from photochemical reactions with sunlight (Tiwary & Colls, 2009). The levels of different atmospheric pollutants are often co-varying. For example, vehicle emissions are responsible for the production of CO, NOx, PM and VOCs; high levels of NOx at a particular location are often correlated with high levels of PM when the dominant source of both pollutants is vehicle exhaust. Vehicle exhaust is also largely responsible for the production of Black Carbon (BC). BC is a component of PM which is associated with smaller traffic-emitted aerosols and is

often better correlated with traffic-related emissions than other PM measurements. Diesel and petrol (gasoline) engines emit these pollutants to differing extents, depending on the emissions control technology used in each (Mi, Lee, Tsai & Chen, 2001); individual engines produce pollutants at very different rates depending on engine temperature, engine load, tuning, age, etc. (Resitoglu, Altinisik & Keskin, 2015).

There are a number of techniques available for measuring PM in the atmosphere, however, due to the complex nature of PM, the method used can significantly influence the data obtained. Available monitoring methods include direct reading instruments – which provide a continuous measure of particle concentration – and filter-based gravimetric instruments – which allow PM to be collected on a filter which is subsequently weighed in a laboratory (see https://uk-air.defra.gov.uk/assets/documents/reports/aqeg/ch5.pdf for full methodology). Measurements of PM are given in units of particle mass per unit volume of air (e.g. $\mu g/m^3$).

'Size distribution' readings correspond to the variation in particle number concentration or mass concentration with particle size; how the particles within the measurement are distributed according to their size. Particles less than 100nm in size are termed 'nanoparticles' or 'ultrafine particulate matter (UFPM)'; particles between 100nm and 2500nm are termed 'fine particles', and those upwards of 2500nm are defined as 'coarse particles'. This distinction is important in studies of human health as particles of different sizes have been shown to be distributed differently throughout the body (Nemmar, Hoet, Vanquickenborne, Dinsdale, Homeer, Hoylaerts, et al., (2001). Distribution of PM within the body according to size will be explored in greater detail later in this report.

Measurements of air pollution can be taken according to 'number concentration' – the number of particles of a given size per unit volume of air – and/or 'mass/volume concentration' – the mass/volume of particles of a given size per unit volume of air. Coarse particles have a greater mass value than fine and ultrafine particles; this is reflected in different readings for number vs. mass concentrations for the same air sample, illustrating the importance of stating the method by which the reported measurements have been made.

(1.2.1) Air Pollution Monitoring

Pollutant concentration in the ambient atmosphere is monitored in an attempt to prevent health problems derived from exposure to particular pollutants. Table 1 outlines the limits and allowed exceedances of global air pollution according to the European Commission.

Table 1 : EC Guidelines for Pollutant Concentration Levels in Europe

Pollutant	Concentration	Averaging Period	Permitted Exceedences Per Year
PM2.5	25 µg/m3	1 year	N/A
Sulphur Dioxide (SO2)	350 µg/m3	1 hour	24
NO2	200 µg/m3	1 hour	18
	40 µg/m3	1 year	N/A
PM10	50 µg/m3	24 hours	35
	40 µg/m3	1 year	N/A
Lead (Pb)	0.5 µg/m3	1 year	N/A
Carbon Monoxide (CO)	10 µg/m3	8 hours	N/A
Ozone	120 µg/m3	8 hours	25 (averaged over 3 years)
Polycyclic Aromatic Hydrocarbons (PAHs)	1 ng/m3	1 year	N/A

Table 1 : EC Guidelines for Pollutant Concentration Levels in Europe

Table 2 (below) shows the annual mean concentration of PM10 for 91 countries worldwide, as generated by the World Health Organisation (WHO, 2016), stratified from the highest to lowest figures. The table also shows how many µg/m^3 each data point is above/below the world average of 71 µg/m^3 per year. It is noteworthy that the largest pool of sampled data came from the United States of America, with comparatively little data available for large countries such as the Russian Federation and China (see Appendix to access full data set).

Country	Annual mean PM10 ug/m3	Above or below world average of 71ug/m3	Year	Reported or calculated mean
Mongolia	279	208	2008	Reported
Botswana	216	145	2005	Calculated
Pakistan	198	127	2003-2004	Calculated
Senegal	145	74	2010	Calculated
Saudi Arabia	143	72	2003	Calculated
Egypt	138	67	2008	Reported
United Arab Emirates	132	61	2008	Calculated
Nigeria	124	53	2006	Reported
Iran (Islamic Republic of)	124	53	2009	Calculated
Kuwait	123	52	2003	Reported
Bangladesh	120	49	2007	Calculated
Bosnia and Herzegovina	117	46	2008	Calculated
India	109	38	2008	Calculated
Nepal	106	35	2005	Calculated
China	98	27	2009	Calculated
Ghana	98	27	2008	Calculated
Myanmar	94	23	2007	Calculated
Bolivia (Plurinational State of)	82	11	2007	Calculated
Tunisia	80	9	2006	Calculated
Sri Lanka	77	6	2008	Reported
Peru	74	3	2010	Calculated
Colombia	71	0	2005-2007	Calculated
The former Yugoslav Republic of Macedonia	70	-1	2008	Calculated
Madagascar	68	-3	2003	Calculated
Turkey	66	-5	2008	Calculated
United Republic of Tanzania	64	-7	2005-2006	Calculated
Chile	62	-9	2007-2008	Calculated
Republic of Korea	61	-10	2007	Calculated
Bulgaria	60	-11	2008	Calculated
Israel	59	-12	2009	Calculated
Indonesia	55	-16	2008	Calculated
Mexico	55	-16	2009	Calculated
Cyprus	53	-18	2007	Calculated
Lebanon	53	-18	2004	Calculated
El Salvador	52	-19	2007	Calculated
South Africa	52	-19	2009	Calculated
Guatemala	48	-23	2008	Calculated
Jamaica	48	-23	2008	Calculated
Philippines	47	-24	2007	Calculated
Greece	44	-27	2008	Calculated
Serbia	43	-28	2008	Calculated
Algeria	42	-29	2006	Reported
Malaysia	42	-29	2008	Reported
Romania	42	-29	2008	Calculated
Thailand	41	-30	2008	Reported
Venezuela	41	-30	2008	Reported

Brazil	40	-31	2009	Calculated
Panama	40	-31	2009	Calculated
Latvia	39	-32	2008	Calculated
Uruguay	39	-32	2009	Reported
Argentina	38	-33	2010	Calculated
Italy	37	-34	2008	Calculated
Ecuador	35	-36	2009	Calculated
Malta	35	-36	2007	Calculated
Croatia	33	-38	2008	Calculated
Poland	33	-38	2008	Calculated
Russian Federation	32.5	-38	2009	Calculated
Singapore	32	-39	2009	Reported
Slovenia	30	-41	2008	Calculated
Czech Republic	29	-42	2008	Calculated
Spain	29	-42	2008	Calculated
Costa Rica	28	-44	2007	Calculated
Portugal	28	-43	2008	Calculated
Denmark	27	-44	2008	Calculated
France	27	-44	2008	Calculated
Hungary	27	-44	2008	Calculated
Slovakia	27	-44	2008	Calculated
Belgium	26	-45	2008	Calculated
Netherlands	26	-45	2008	Calculated
Austria	25	-46	2008	Calculated
Germany	25	-46	2008	Calculated
Sweden	25	-46	2008	Calculated
Belarus	24	-47	2008	Calculated
Iceland	24	-47	2008	Calculated
United Kingdom	23	-48	2008	Calculated
Japan	22	-49	2008	Reported
New Zealand	22	-49	2009	Calculated
Norway	22	-49	2008	Calculated
Switzerland	22	-49	2008	Calculated
Lithuania	21	-50	2008	Calculated
San Marino	20	-52	2009	Calculated
Finland	19	-52	2008	Calculated
Bhutan	18	-53	2006	Reported
Luxembourg	18	-53	2008	Calculated
Monaco	18	-53	2008	Calculated
United States of America	18	-53	2008	Reported
Ireland	15	-56	2008	Calculated
Australia	13	-58	2009	Calculated
Canada	13	-58	2008	Calculated
Mauritius	12	-59	2009	Calculated
Estonia	11	-60	2008	Calculated

Table 2. Annual mean concentration of PM10 for 91 countries worldwide, as generated by the World Health Organisation (WHO, 2016), stratified from the highest to lowest figures. The United Kingdom is highlighted in yellow.

In the UK, there are a number of existing guidelines which set objectives for local authorities with regards to their air quality management duties. These are set out by Air Quality (England) Regulations 2000 and the Air Quality (England) (Amendment) Regulations 2002 (HMG, 2002a). Reference is also made to the Air Quality Standards Regulations 2010 (HMG, 2010), The Environment Act 1995 (1995) and relevant aspects of the European Union directive 2008/50/EC (EC, 2008). Table 1 illustrates the standards imposed by the European Commission (EC) with regards to pollutant levels in the EU. The EC adopted a Clean Air Policy Package in December 2013, consisting of A New Clean Air Programme for Europe with new air quality objectives for the period up to 2030 (EC, 2013). The current limit for NO2 in the UK is 40µg/m^3 annual average, and the hourly average should not exceed 200µg/m^3 per hour more than 18 times a year (Thornes et al. 2016) (*see Table 1*).

However, statistics provided by DEFRA show some areas of the UK to persistently exceed these levels. Indeed, in 2016, the average NO2 concentration at Stoke-on-Trent A50 Roadside was 59.87µg/m^3 and on Oldbury Birmingham Road was 39.65 µg/m^3 (DEFRA statistics, accessed 11/1/17). Furthermore, a campaign by Friends of the Earth Birmingham recently claimed that 7 sampled locations within the city exceeded the EU limits for nitrogen dioxide (NO_2). The group also claimed that a high number of roads within the city are not predicted to achieve the legal nitrogen dioxide (NO_2) limit before 2030 and that NO2 levels on some roads are not predicted to reach safe levels until 2023 (https://www.birminghammail.co.uk/news/midlands-news/revealed-birminghams-worst-air-pollution-7656074 accessed 03/05/18). In a 3-month monitoring of the newly renovated Birmingham New Street Station, NO_2 was found to exceed 40µg/m_3 in all locations (all platforms, concourse and stairways) (Thornes, 2016). In London, NO_2 figures are often even higher; London Marylebone Road showed an average annual NO2 concentration of 87.06 µg/m^3 in 2016 (DEFRA statistics, accessed 11/1/17), more than double the recommended annual limit.

Another regulated pollutant is PM2.5. The term 'PM' is used to describe the mixture of solid particles and liquid droplets suspended in the air; these can be either man-made or naturally occurring. The PM which is referred to in this report is that which is produced by man-made sources, most commonly from vehicle emissions. PM varies in size (i.e. the diameter of the particle, usually measured by its aerodynamic characteristics); PM2.5 refers to the mass concentration (in µg/m^3) of particulate matter with a diameter of 2.5 µm or less. As vehicle emissions are the most prolific source of PM2.5, levels of the pollutant are often much higher close to roadsides and in urban areas than in rural and remote

environments. The EC guidelines for PM2.5 levels stipulate that the annual average concentration should not exceed 25 µg/m^3 (*see Table 1*). Average annual levels of PM2.5 in the UK do not often exceed this level, however, there is understood to be no safe threshold below which no adverse effects would be anticipated (http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf) and some parts of the UK have shown high levels of the pollutant during some periods. For example, a monitoring site in Leamington Spa reached 52 µg/m^3 on 12/3/16; 27 µg/m^3 above the EC guideline hourly limit. On the same day, London Marylebone Road reached 75 µg/m^3; 50 µg/m^3 above the hourly limit (DEFRA statistics, accessed 11/1/17).

Ultrafine Particulate Matter/UFPM (<0.1 µm in diameter) contributes very little to particle mass and therefore requires measurement as a number concentration, rather than by mass concentration as for PM10 and PM2.5. In the UK, the Condensation Particle Counter (CPC) is commonly used to count UFPM between 0.003 µm and 2.0 µm in an optical detector. Regulations do not currently exist for UFPM as they do for PM2.5 and PM10 and the health effects of exposure to this size class of particles are not well known. The current difficulties in applying legislation to levels of UFPM in the ambient atmosphere relate to the scientific complexity of exposure assessment (e.g. appropriate instrumentation and measurement, post-inhalation effects and interpretation of data) (http://apps.who.int/iris/bitstream/10665/67338/1/a76621.pdf).

(3) Assessing Exposure to Air Pollution

Quantifying exposure to air pollution in a naturalistic setting provides a significant challenge to research. In the UK, high quality short-term data is only available at specific monitoring stations (e.g. the 12 within the West Midlands outlined in Table 3, below); data for the areas located away from these stations is usually generated using modelled data and therefore only represents predicted values.

24 Hour Summary						
Monitoring site	**Running 8 Hour mean**	**Hourly mean**	**Max 15 min mean**	**Running 24 Hour mean**	**Running 24 Hour mean**	**Last updated**
	Ozone (µgm-3)	*Nitrogen dioxide (µgm-*	*Sulphur dioxide (µgm-*	*PM2.5 (µgm-3)*	*PM10 (µgm-3)*	
Birmingham A4540 Roadside	50 (2 Low)	76 (2 Low)	n/m	8 (1 Low)	20 (2 Low)	11/01/2017
Birmingham Acocks Green	60 (2 Low)	38 (1 Low)	n/m	12 (2 Low)	n/m	11/01/2017
Birmingham Tyburn	n/a	n/a	n/a	9 (1 Low)	21 (2 Low)	11/01/2017
Cannock A5190 Roadside	n/m	39 (1 Low)	n/m	n/m	n/m	11/01/2017
Coventry Allesley	60 (2 Low)	40 (1 Low)	n/m	8 (1 Low)	n/m	11/01/2017
Leamington Spa	65 (2 Low)	36 (1 Low)	n/m	9 (1 Low)	13 (1 Low)	11/01/2017
Leamington Spa Rugby Road	n/m	30 (1 Low)	n/m	9 (1 Low)	16 (1 Low)	11/01/2017
Leominster	n/a	n/a	n/m	n/m	n/m	11/01/2017
Oldbury Birmingham Road	n/m	79 (2 Low)	n/m	n/m	n/m	11/01/2017
Stoke-on-Trent A50 Roadside	n/m	96 (2 Low)	n/m	n/m	19 (2 Low)	11/01/2017
Stoke-on-Trent Centre	67 (3 Low)	48 (1 Low)	n/m	7 (1 Low)	n/m	11/01/2017
Walsall Woodlands	71 (3 Low)	33 (1 Low)	n/m	n/m	n/m	11/01/2017

Table 3: 24-hour summary of air pollution concentration at 12 monitoring sites within the West Midlands

There are a number of different types of model which exist for predicting pollutant concentration. Deterministic models calculate pollutant concentration based on measured data from emissions inventories and meteorological variables (e.g. wind speed and direction, geography of the land). Statistical models estimate pollutant concentration using statistical equations to describe the relationship between a series of predictors. For example, Zhong, Cai and Bloss (2016) have applied a coupled two-box model approximation to describe how particles might be distributed within a street canyon. The authors note a significant pollutant contrast between the lower and upper parts of a deep street canyon, particularly for NO_2, meaning that a classic one-box model (which assumes a well-mixed atmosphere at all heights within the canyon) is inappropriate. By applying a model which consists of two segregated boxes (one upper; one lower), the authors were able to predict a more accurate NO_2 value. Such models are able to predict area source emissions, that is, the pollutant concentration across a given area. Point source emissions employ a Gaussian equation to predict the spatial and temporal distribution of pollutants which are produced at a single point e.g. a factory burning fossil fuels. Line

source emissions (e.g. motorways) can be calculated using a series of point source analyses or using a line source approximation. It is necessary to keep in mind that such predictions are frequently used in place of measured data in the reporting of emissions; both modelled and measured data is referenced and appropriately indicated in this report.

Furthermore, neither measured nor modelled atmospheric data is able to quantify the exact exposure an individual receives. Portable monitoring instruments (e.g. passive badge samplers [Brown et al. 1995, 2000] and portable CPCs) are increasingly being developed in order to obtain more accurate personal exposure data. Such instruments seek to sample air from the 'breathing zone' of an individual – approximately 30 cm from the nose and mouth – and are designed to move through changing microenvironments with the wearer (https://uk-air.defra.gov.uk/assets/documents/reports/aqeg/ch5.pdf). Such instruments aim to provide a personalised exposure value for the individual which might characterise better the particle mass/number concentration inhaled. The time resolution for high-volume sampling using such instruments is usually limited to 24-hours; there is limited research available confirming their efficacy for assessing chronic exposure.

It is noteworthy that even if atmospheric conditions could be characterised perfectly using measured and/or modelled data, the respirable fraction of atmospheric pollution – that is, the amount which successfully enters the respiratory tract of an individual – is almost impossible to measure. It has been suggested that PM of different sizes may be deposited at different sites within the respiratory tract (Cahill, Ashbaugh, Barone, Eldred, Feeney, Flocchini et al., 2017). Sequential filtration techniques have shown coarse particles (PM10, PM2.5) to be deposited mainly in the upper respiratory tract and fine particles (UFPM) to be deposited mainly in the lower respiratory tract (Cahill et al., 2017). Further research has shown that PM can be deposited in the lungs in a number of ways and that the size of these particles partially determines how and where this takes place (Carvalho, Peters and Williams III, 2011). For example, airborne particulates which possess enough momentum to remain on their trajectory despite changes in the direction of the airway will collide with the walls of the respiratory tract. Therefore, particles with a diameter of 10 µm or more usually impact in the nose or throat and are deposited there. In contrast, some particles which enter the respiratory tract are influenced by gravity and settle on the surrounding walls (i.e. during breath holding). This process is termed 'sedimentation' and is relevant to particles measuring between 0.5 µm and 5 µm. Such particles are deposited in this

way in the surface of the lungs (usually in the bronchi and bronchioles). Some particles are sufficiently small (0.5 µm and smaller) to undergo random motion (Brownian motion or 'diffusion'), due to molecular bombardment. The movement of these particles within the respiratory system is difficult to predict. Indeed, there is limited evidence regarding the exposure-response relationship for particles of this size, but significant health implications have been predicted by a number of commentators (*see http://apps.who.int/iris/bitstream/10665/67338/1/a76621.pdf for summary*).

(4) An Introduction to the Health Effects of Exposure to Air Pollution

The biggest impact of particulate air pollution (AP) on public health is understood to be from long-term exposure to PM2.5, which increases the age-specific mortality risk, particularly from cardiovascular effects (DEFRA factsheet, accessed 11/1/17). Indeed, previously explored health effects of exposure to AP focus closely on cardiovascular disease, as well as cancer, asthma, stroke and some incidences of immune system and birth defects (Passchier-Vermeer & Passchier, 2000).

Clinical and epidemiological studies show that long term exposure to air pollution increases mortality from cardiovascular and respiratory diseases (Fiordelisi, Piscitelli, Trimarco, Coscioni, Iaccarino & Sorriento 2017). For example, a cohort study from 1990 estimated that short term exposure to PM2.5 increases the risk of a cardiovascular event from 0.4% to 1.0% in healthy adults (Schlesinger, 2007). Furthermore, in the Air Pollution and Health: a European Approach (APHEA) study, increases in SO_2 and PM10 were associated with a 0.4% increase in the rate of cardiovascular mortality (Katsouyanni, Touloumi, Spix, Schwartz, Balducci, Medina et al., 1997). Elderly patients, children and individuals with pre-existing cardiovascular conditions show greater vulnerability to such effects. For example, in 2006 elderly residents of 21 US cities showed a 0.65% increased risk of hospitalisation for myocardial infarction per 10 µg/m^3 increase in PM10 in comparison with healthy adult residents (Polichetti, Cocco, Spinali, Trimarco & Nunziata, 2009). The increased risk of myocardial ischemic injury following short-term exposure to PM has been attributed to increased systematic inflammation, altered endothelial function, enhanced thrombotic tendency and atrial fibrillation (Fiordelisi et al. 2017). Long-term exposure to increased levels of PM2.5 have been associated with up to a 13% increased risk of coronary events, even when the levels of PM2.5 measured are below the current European limit values (25 µg/m^3) (Cesaroni, Forastiere, Stafoggia, Andersen, Badaloni, Beelen et al. 2014). It has been

suggested that long term exposure to PM2.5 could promote the development of cardiometabolic disorders which, in turn, cause an increased risk of cardiovascular injury (Fiordelisi et al. 2017).

Positive associations have also been found between long-term exposure to PM and lung cancer mortality (Turner, Krewski, Pope III, Chen, Gapstur & Thun, 2011). In this prospective study, each 10 $\mu g/m^3$ increase in PM2.5 concentration was associated with a 15 – 27% increase in risk of lung cancer mortality in 'never-smokers'. This finding was maintained after adjustment for passive smoking, occupational exposure, exposure to radon and potential socioeconomic confounders and was stronger in individuals with a history of asthma. It is this, and other such findings, which have caused the International Agency for Research on Cancer (IARC) to classify outdoor air pollution exposure as a Group 1 carcinogen and provide justification for the use of government-imposed limit values.

Further research suggests that carbon monoxide (CO) absorbed during inhilation reduces the capacity to transport available oxygen to the lungs (Khare & Shiva Nagendra, 2007). Furthermore, CO has been found to bond to haemoglobin and form COHb which reduces the levels of oxygen within the blood (Khare et al., 2007). NO_2 has been shown to be absorbed into the mucous membrane of the respiratory tract and increase susceptibility to respiratory infection. Interestingly, the upper airway has been shown to be less affected by this, potentially because NO_2 has reduced solubility to aqueous surfaces.

(5) Air Pollution and Cognitive Function

Increasing evidence also links exposure to air pollution to Central Nervous System (CNS) disease, cognitive impairment and neuropathology in mammals (Block and Calderon-Garciduenas, 2009). Current literature has utilised in vitro, in vivo and epidemiological procedures to begin shedding light on these effects and to speculate upon their potential mechanisms. However, much is still unknown; the aim of this review is to outline the current position of the literature with regards to the relationship between air quality and cognition and to establish the requirements and goals of future research.

Preliminary evidence exists which links acute and chronic AP exposure to reduced scores on some cognitive tasks (Ailshire & Clarke, 2015; Allen, MacNaughton, Satish, Santanam, Vallarino & Spengler, 2016; Chen & Schwartz, 2009; and Harris, Gold, Rifas-Shiman, Melly, Zanobetti, Coull, Schwartz, et

al., 2015), markers of neurodegenerative disease (Calderon-Garciduenas, Azzarelli, Acuna, Garcia, Gambling, Osnaya et al., 2002; Calderon-Garciduenas, Reed, Maronpot, Henriquez-Roldán, Delgado-Chavez, Calderon-Garciduenas et al., 2004; Moulton & Yang 2012; and Willis, Evanoff, Lian, Galarza, Wegrzyn, Schootman, & Racette, 2010) and neurodevelopmental disorders, especially autism (Becerra, Wilhelm, Olsen, Cockburn, & Ritz, 2013; Volk, Hertz-Picciotto, Delwiche, Lurmann, & McConnell, 2011; and Windham, Sumner, Li, Anderson, Katz, Croen, & Grether, 2013).

(1.6) Cognitive Measures

The effects of AP on cognitive function have been measured in a growing number of studies. Focus on the correlation between current or prenatal exposure to AP and the results of cognitive or neuropsychological tests has provided useful indication that AP may be detrimental to cognitive performance. Controlled exposures to predetermined concentrations of various air pollutants, compared with subsequent performance on cognitive tasks have also characterised a possible link between these variables.

(1.7) Correlational studies

Some studies have sought to correlate modelled exposure to AP with performance on cognitive tasks. Dispersion models are often used to provide an estimate of AP concentration at a particular location; these models can be used to estimate exposure to particular AP components at participants' locations. This data can subsequently be correlated with assessments of cognitive function in order to infer relationship.

Postcode sampling is a recruitment technique which allows experimenters to obtain a participant group with a particular set of demographics. In the study of the effects of air quality, sampling individuals from particular locations allows the creation of distinct groups of participants who are exposed to either high or low levels of AP in a naturalistic setting. The cognitive performance, health etc. of individuals within each of these categories can then be compared. This technique is useful because it allows the recruitment of participants who already fit the relevant criteria for the study; groups can be designed so as to be suitably distinct from one another without the need for researchers to perform experimental manipulations (e.g. directly exposing groups of individuals to polluted air) for the purpose of the study.

The modelled annual NO_2 concentration for the region of Greater London is given below (Figure 2). To obtain a participant sample who were regularly exposed to high levels of air pollution, researchers could sample individuals who resided in the area marked in red (the A4202); to obtain a group of individuals with a lower everyday exposure to AP, experimenters could sample individuals who resided in the area marked in black (Queens Park area).

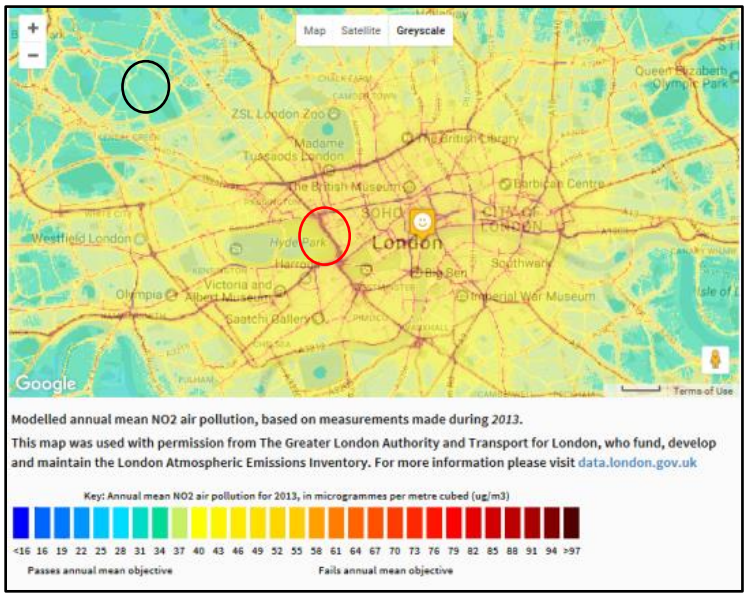

Figure 2: Modelled annual NO_2 concentration for Greater London (2017)

A number of studies have found evidence for a relationship between AP exposure and cognitive function using correlational techniques. For example, reduced performance on psychomotor, attention and sensory scales has been recorded in children residing in areas with high measured levels of NO_2, in comparison with children from 'cleaner' areas (Wang, Zhang, Zeng, Zeng, Wang, & Chen, 2009). Exposure to Black Carbon (BC), a marker for traffic pollution, has also been linked with lower verbal and non-verbal IQ and reduced visual memory function in 8 – 11-year-old children (Suglia, Gryparis, Wright, Schwartz & Wright, 2008). Furthermore, proximity to major roadway during the 3rd trimester of pregnancy and at birth is correlated with reduced scores on verbal IQ, non-verbal IQ and visual memory measures at 8 years old. This finding remained robust after controlling for socioeconomic and

demographic variables (Harris et al., 2015). These findings suggest that exposure to traffic-related AP may be detrimental to cognitive development. Interestingly, levels of BC exposure at 8 years old only (and not during pregnancy and/or at birth) do not predict reductions in verbal IQ (Harris, 2015). This may suggest a sensitive period during prenatal and early-life, during which individuals may be more vulnerable to the effects of AP exposure on cognitive function. AP exposure during pregnancy has also been linked with preterm birth and intrauterine growth restriction (Stieb, Chen, Eshoul & Judek, 2012), both of which show inverse associations with cognitive development (Shenkin, Starr & Deary, 2004). However, the relationship between AP exposure, birthweight and/or gestation length and cognition is not clear (Harris et al., 2015). Therefore, pregnancy, particularly the 3rd trimester, is potentially a sensitive period for the adverse effects of AP on cognitive development but the mechanism by which this might be the case remains unclear.

Higher PM10 exposure values have been correlated with reduced performance on reaction time tasks (RTT), symbol-digit substitution tests (SDST) and serial-digit learning tasks (SDLT) (NES2; Chen & Schwartz, 2009). In this study, using residential data from the NHANES-III study (Hollowell, Staehling, Flanders, Hannon, Gunter, Spencer, & Braverman, 2002) and annual PM10 exposure data from EPA (AIRS), participants were assigned AP exposure values which were correlated with the results from the 3 cognitive function tests (NES2). The aforementioned effects remained after adjustment for age and sex. However, the association became non-significant after adjusting for race/ethnicity and SES. This suggests that the relationship between PM10 and cognitive function may not be straightforward. However, higher estimated exposure values to O3 were significantly correlated with SDST and SDLT performance both before and after adjustment for age, sex and race. Furthermore, the correlation between O3 and SDLT remained after adjustment for SES, suggesting that O3 exposure has a detrimental effect on cognitive performance regardless of these other variables.

It is noteworthy that socioeconomic status (SES) may also have an effect on overall health. Factors which contribute to an individual's socioeconomic status may include financial standing, educational opportunities, familial and ethnic background, residential location, health status, employment status and relationship/friendship networks. It is assumed that access to resources such as financial prosperity, employment etc. enables groups/individuals to prosper within a social world. The link between SES and health is much reported on in the psychological literature, yet the relationship between these two variables remains unclear. One position is that individuals with greater physical and

mental wellbeing rise to the top of the social scale and are able to flourish within society; those with lower physical and mental wellbeing descend the social ladder and subsequently have reduced access to financial, educational and employment opportunities. A second position posits that those with higher SES receive greater access to healthcare and are able to finance activities which enable them to achieve physical and mental wellbeing (e.g. access to private healthcare, gym facilities etc.).

(1.7.1) Neurodevelopmental disorder

Neurodevelopmental disorders are characterised by specific impairments to the function of the brain and central nervous system which manifest early in development, often before a child has entered formal education. These impairments often produce deficits in social, emotional, academic and/or occupational functioning and can range from very specific impairments – such as in attentional control in children diagnosed with ADHD – or more general limitations to everyday functioning, such as in Autistic Spectrum Disorders (ASD). ASD are characterised by a number of social and emotional impairments such as deficits in social communication and social interaction, restrictive and repetitive patterns of behaviour and/or interests and hyper- or hypo-reactivity to sensory input (e.g. an apparent indifference to pain/heat/cold, excessive touching of objects, fascination with lights or spinning objects) (Lauristen, 2013). Crucially, in order to distinguish ASD and other neurodevelopmental disorders from general cognitive impairment in adulthood, these symptoms must be presented in early childhood, usually before the child is 3 years old.

The literature yields some exploration of the link between AP exposure and neurodevelopmental disorder. Children of mothers living within 309 metres of a freeway during pregnancy show a greater likelihood of Autism Spectrum Disorder (ASD) diagnosis than children of mothers living more than 1,419 metres away (Volk, 2011). In this study, in order to determine exposure cut-points, the distribution of distance from the nearest freeway among all 563 subjects (304 ASD cases and 259 controls) was examined. The cut-points defined the closest 10% (< 309 m), the next 15% (309–647 m), and the next 25% (647–1,419 m) as exposure groups. The remaining 50% (> 1,419 m) served as the reference group. Only the top 10% (those living within 309m of a freeway at birth) showed an association with ASD diagnosis compared with those living further away. This relationship was not

altered by adjusting for sex, race, maximum education in the home, maternal age, or maternal smoking during pregnancy.

Exposure to O_3 in the 2nd and 3rd trimesters of pregnancy has also been associated with ASD diagnosis (Becerra, 2013). Indeed, Becerra et al. (2013) report that a 11.54ppb increase in O3 exposure during pregnancy increased the likelihood of having a child diagnosed with ASD by 6-12% (Becerra, 2013). It is noteworthy that high levels of NOx can lead to O_3 being depressed below background levels in urban areas; the highest levels of ozone are often in the far suburbs.

Exposure to air pollution has also been linked with diagnoses of ADHD (Fleugge, 2016). ADHD (Attention Deficit Hyperactivity Disorder) is distinct from ASD in that the main symptoms of the disorder are seen in attentional and inhibitory responses, rather than in social and emotional functioning. Children with ADHD display problems with inattentiveness (e.g. having a short attention span, appearing forgetful, constantly changing activity or task), hyperactivity and impulsiveness (e.g. fidgeting, poor concentration, excessive talking and physical movement, little or no sense of danger). In the review by Fleugge (2016), exposure to nitrous oxide (N_2O) in particular was considered to be the 'principle exposure' contributing to ADHD development. and is thought to target the neural substrates of opioidergic, dopaminergic, glutamatergic and cholinergic systems. Indeed, exposure to N_2O via use of gas appliances in the home has been shown to have a negative linear relationship with adverse cognitive effects represented in ADHD (Moralez, Julvez, Torrent, Cid, Guxens, Bustamante et al. 2009). The author suggests that chronic exposure to environmental N2O induces a parasympathetic dominant state through inhibition of a7AChR (which enhances glutaminergic firing that potentiates working memory and attention-related circuitry in the Prefrontal Cortex – the area of the brain responsible for problem solving, decision making and generating complex thought) and dysregulation of dopamine. This suggests that exposure to AP may contribute to the development of ADHD. It is noteworthy that N_2O is not usually considered to be a pollutant and is not subject to threshold limit values. It occurs in small amounts in the atmosphere but follows a different distribution pattern to that of NOx and PM; highest levels are usually found in rural areas.

(1.7.2) Neurodegenerative disease

Alzheimer's disease (AD) is a neurodegenerative disease of growing prevalence amongst an aging population. The earliest symptoms of the disease usually involve loss of basic memory functions particularly the recall of recent events and the learning of new information. This pattern of memory loss occurs because the hippocampus, the brain structure responsible for such facets of memory, is extremely vulnerable to age-related degeneration. AD is characterised by two neuropathological hallmarks: a dysfunction of the amyloid cascade inducing deposition of extracellular amyloid plaques in the brain and hyperphosphorylation of tau protein which forms intracellular neurofibrillary tangles. In turn, the build-up of proteins which form plaques and tangles in the brain leads to the loss of connections between nerve cells, and eventually to the death of nerve cells and loss of brain tissue; contributing to neurodegeneration (*see figure 3*). This process appears to occur first in the hippocampus; accounting for the gradual loss of memory function symptomatic of AD. This process has also been found to be associated with increased inflammatory mechanisms and accruing oxidative stress (Alles et al. 2012).

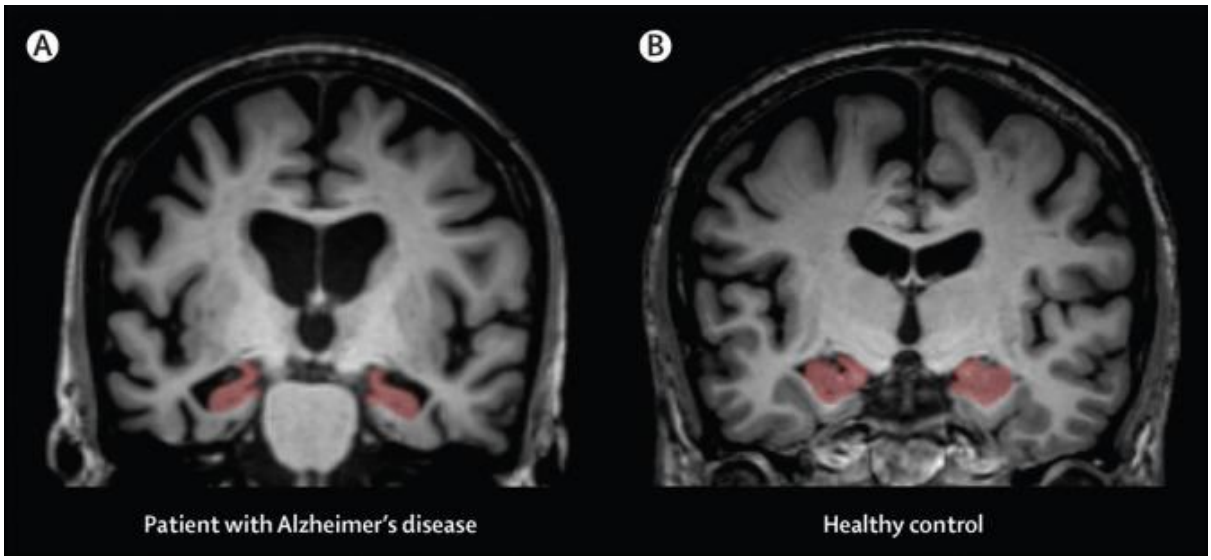

Figure 3: Coronal sections shown from high-resolution structural MRI scans depicting the head of the hippocampus (labelled in red) in a patient with Alzheimer's disease (A) and a healthy age-matched control (B). Severe atrophy of the hippocampus in the patient with Alzheimer's disease is evident by visual comparison with the healthy control (Teipel, Drzezga, Grothe, Barthel, Chetelat, Schuff et al., 2015)

Markers of neurodegenerative disease are elevated in individuals exposed to high levels of AP. For example, post-mortem examination of the brains of feral dogs from Mexico City showed upregulation of COX2 expression (indicative of chronic inflammation and a feature of clinical progression to early Alzheimer's Disease) as well as accelerated accumulation of AB-42, a clinical marker of AD (Calderon-Garciduenas et al., 2002). Furthermore, autopsies of the brains of human Mexican subjects also showed an elevation of COX2 mRNA levels, especially in the hippocampus, of individuals who were residents of highly polluted cities (Calderon-Garciduenas et al., 2004). Subchronic diesel exhaust (DE) exposure is also linked to increases in Tau in frontal and temporal lobes (Levesque, Taetzsch, Lull, Kodavanti, Stadler, Wagner et al., 2011). Increases in Tau phosphorylation at the Ser 199 residue (Tau[S199]) have been linked with neurofibrillary tangles implicated in AD pathology. This suggests that chronic exposure to AP may contribute to the progression to AD pathology in humans.

(1.7.3) Summary of Correlational Studies

Therefore, correlational studies have provided some important preliminary and circumstantial evidence linking AP exposure to cognitive impairment. The findings suggest that exposure to certain AP components during pregnancy and early life may be detrimental to normal cognitive development. Furthermore, long-term residential exposure to AP may affect aspects of cognitive function including attention and learning mechanisms and may be linked to neurodegeneration. However, a major limitation of this method is that lack of accuracy in determining exact AP exposure. Estimating exposure based on concentration data from monitoring equipment near to participants' homes may not adequately capture real-life exposure. Furthermore, this method fails to consider time spent away from the home; participants may live in an area with low AP levels but commute to work every day in heavy traffic, or indeed work in an area with high levels of AP. Therefore, postcode sampling does not accurately account for everyday exposure levels. Additionally, environmental AP contains multiple chemicals and particles which may act differentially on performance; using this method, particular AP compounds which may be affecting cognitive performance cannot be known. This method also assumes chronic inflammation is the mechanism by which cognitive function may be reduced; persistent exposure to particular AP levels at a participant's home cause long-term changes in cognitive wellbeing as opposed to acute, moment-to-moment exposures causing temporary decline. Separating chronic from acute effects should be a key aim of future research.

(1.8) Exposure studies

Exposure studies seek to manipulate directly the composition of inhaled air in order to establish exposure effects of different AP components. Exposure has been achieved by direct inhalation of AP compounds in rodent models (Levesque et al., 2011) and controlled exposure to particular concentrations of substances via pump/filtration methods in humans (Allen et al., 2015; Crüts, van Etten, Törnqvist, Blomberg, Sandström, Mills & Borm, 2008; Satish, Mendell, Shekhar, Hotchi, Sullivan, Streufert & Fisk, 2012).

(1.8.1) Rodent Studies

Daily intranasal exposure to PM over 2 weeks in asthmatic mice has been linked with increased expression of pro-inflammatory cytokines (NF-kB and IL-1a; cytokines are described in more detail in section 1.10.1, below) and chronic inflammation, a marker for neurodegeneration (Campbell, Oldham, Becaria, Bondy, Meacher, Sioutas, et al., 2005). 6-month exposure to DE has also been linked to increased pro-inflammatory cytokine TNF-a expression in the brains of mice (Levesque et al., 2011). In this study, TNF-a expression was increased in the olfactory bulb (a hypothesized point of entry of PM in the brain), frontal lobe, temporal lobe and midbrain in response to the highest concentration of DE (992 µg PM m^{-3}). It is noteworthy that this is a very high dose of DE, even for countries with elevated annual readings (see Table 1, Section 1.2.1) and illustrates that toxicity studies often mimic chronic exposure via acute doses of a pollutant. The midbrain also exhibited increased TNF-a levels at 311 µg PM m^{-3} DE, and 100 µg PM m^{-3} DE, indicating a greater sensitivity to the pro-inflammatory effects of DE. Furthermore, increased Tau phosphorylation has been measured in the frontal and temporal lobes of mice exposed to DE (Levesque et al., 2011). Tau is hyper-phosphorylated at several sites during the course of some neurodegenerative diseases, and elevation of Tau phosphorylation at Tau [pS199] has been specifically linked to neurofibrillary tangles associated with AD. Levesque (2011) found Tau [pS199] levels to be significantly increased from control at 311 and 992 µg PM m^3 in the temporal lobe and at 992 µg PM m^3 DE in the frontal lobe. 992 µg PM m^3 DE exposure also results in significant elevation of a-synuclein protein in the midbrain (Levesque et al., 2011). These findings clearly link DE exposure with clinical markers of neurodegenerative disease.

A study by Saber et al (2006) found DE inhalation to lead to the production of proinflammatory cytokines in mice. Proinflammatory cytokines are produced as a natural response to invasion by an infectious agent or toxin. Although essential to prevent infection, excessive or prolonged production of proinflammatory cytokines can cause cell damage; this will be discussed in greater detail in section 1.10.1 below. Saber, Jacobsen, Bornholdt, Kjær, Dybdahl, Risom et al. (2006) found 80 mg/m^3 inhalation of DE particles lead to a 3-fold increase in TNF levels from baseline 1 day after exposure and a 9-11-fold increase in IL-6 expression within the first 6 hours. The authors suggest that different proinflammatory cytokines may operate within different time frames. They conclude that TNF is not important in early DE-induced inflammation and that other signalling pathways, such as MCP-1, may be more important.

Studies by Dantzer, O'Connor, Freund, Johnson and Kelley (2008), Ekdahl, Claasen, Bonde, Kokaia and Lindvall (2003), Gibertini (1995) and Monje, Toda and Palmer (2003) all use rodent models to examine the effects of neuroinflammation on cognition. See Section 1.10.1 below for more detail on these studies.

(1.8.2) Human Studies

Only a few studies have directly manipulated air quality in order to measure cognitive effects in humans. One of these reported cognitive function to be reduced when CO_2 concentrations were increased (Allen et al., 2015). CO_2 is not generally considered a toxic pollutant in ambient air, although, because vehicle exhaust contains CO_2 and toxic air pollutants, CO_2 is often correlated with the pollutants that are the focus of a study. In the Allen et al. (2015) study, participants were exposed to one of three steady-state CO_2 concentrations on each of 6 days over a two-week period; 550ppm with 100% outdoor air ventilation (‘Green+’ days), 945ppm with 50% outdoor air ventilation (‘Green’ days) or 1400ppm with 50% outdoor air ventilation (‘Conventional’ days). Note that the global average CO_2 level is a little above 400 ppm (https://www.esrl.noaa.gov/gmd/ccgg/trends/, last accessed 03/05/18). At the end of each exposure day, participants completed a computer-based higher-order decision making assessment (Strategic Management Simulation, Streufert et al. 1988) which provided scores on nine different cognitive scales (see Figure 4) Participants were required to respond to scenarios which were based on real-world equivalent challenges (e.g. handling a township in the role of a mayor);

this test is designed to test the effectiveness of management-level employees based on measurements of higher-order decision making. The findings indicate that overall participants showed significantly lower SMS performance (<50%) on Conventional days than on Green and Green+ days. Cognitive function scores were elevated 61% on Green and 101% on Green+ days in comparison with Conventional days. The greatest effects were found for crisis response, information usage and strategy. The authors conclude that high-level CO_2 exposure may affect productivity and responsiveness in the workplace.

Cognitive Function Domain*	Description
Basic Activity Level	Overall ability to make decisions at all times
Applied Activity Level	Capacity to make decisions that are geared toward overall goals
Focused Activity Level	Capacity to pay attention to situations at hand
Task Orientation	Capacity to make specific decisions that are geared toward completion of tasks at hand
Crisis Response	Ability to plan, stay prepared, and strategize under emergency conditions
Information Seeking	Capacity to gather information as required from different available sources
Information Usage	Capacity to use both provided information and information that has been gathered toward attaining overall goals
Breadth of Approach	Capacity to make decisions along multiple dimensions and use a variety of options and opportunities to attain goals
Strategy	Complex thinking parameter that reflects the ability to use well-integrated solutions with the help of optimal use of information and planning
**See Streufert et al. (1986) for detailed descriptions.*	

Figure 4. Description of cognitive domains tested in the Strategic Management Simulation assessment used by Allen et al. (2015). Adapted from https://ehp.niehs.nih.gov/wp-content/uploads/124/6/ehp.1510037.t004.html

In a similar study, cognitive function was also measured using the SMS. Participants were exposed to elevated CO2 and VOC levels for 2.5 hour periods, once a day for 6 days. CO2 exposure at 1000ppm provided SMS raw scores at an average of 11-23% lower than when the exposure level was 600ppm CO2; exposure to CO2 at 2500ppm yielded SMS scores that were 44-94% lower than 600ppm exposure (Satish et al., 2012) on 7/9 scales. This again finds support for the relationship between heightened AP levels and cognitive function. Interestingly 'Focussed Activity' raw score was

increased at 2500ppm exposure. The authors suggest that this might reflect 'overconcentration'; compensatory increase in level of focus when functioning is made difficult e.g. while under the influence of alcohol. Therefore, they conclude that exposure to high levels of CO2 seems to be detrimental to cognitive performance.

Exposure to DE has also been shown to increase functional changes in brain activity (Cruts et al., 2008). Cruts (2008) exposed participants to DE (300 $\mu g/m^3$) or filtered air (FA) for 1-hour on one of 2 testing days (2-4 days apart). EEG was carried out before, during and after exposure. The results showed no difference between DE and FA conditions in the first 5 minutes of exposure. After 30 minutes of exposure, MPF values began to increase slowly in all subjects, with the strongest effects in the DE condition and at frontal sites (Fp1, Fp2, F3 and F4). Interestingly, the effect continued to increase during the post-experiment recording (i.e. after the participant had been removed from the exposure chamber). This suggests a delayed response to DE in frontal regions which may continue after the cessation of exposure. It is noteworthy however that the authors do not state the composition of the filtered air (i.e. what was removed) which makes it difficult to isolate which aspect of DE might contribute to the MPF pattern.

(1.9) Route of Entry

(1.9.1) Structure of the Nasal Cavity

The nasal passageway provides human beings with warm, humidified air obtained from the ambient environment, protects them from damaging particles, bacteria and viruses and provides them with olfaction (Zhu, Lee, Lim, Lee & Wang, 2011). These functions are associated with airflow through the nasal cavity and are subject to individual variation based on nasal morphology and flow rate (Zhu et al. 2011). Inflammation, allergy, sinusitis, polyps and other nasal diseases can also affect nasal airflow (Zhao & Jiang, 2014). The complex three-dimensional structure of the nasal passage has made characterising airflow challenging and many studies have looked to construct computer simulated models in order to do so (e.g. Kelly, Prasad & Wexler, 2000). Generally, there is a relatively low flow rate (approx. 5 – 10%) through the olfactory slit. This is potentially a defence mechanism against the depositing of harmful particles in this portion of the airway; ultrafine particles, whose transport is dominated by diffusion, tends to deposit in the lower part of the airway (Kelly et al. 2000). Low flow rates

have also been recorded in the nasal meatuses and highest velocities have been recorded in the nasal valve and along the floor of the nasal cavity in the inferior airway.

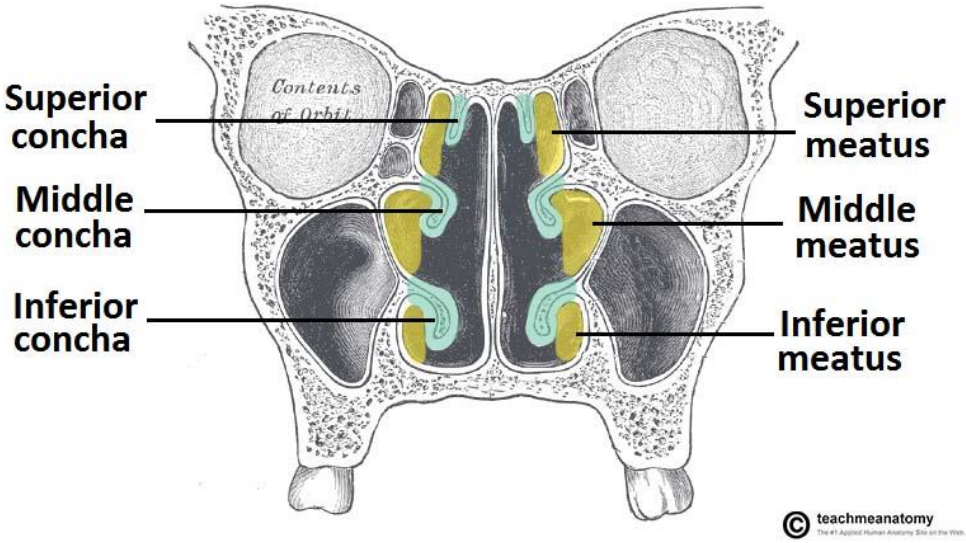

Figure 5: Coronal section of the anterior nasal cavity. http://teachmeanatomy.info/head/organs/the-nose/nasal-cavity/ (accessed 02/04/2018)

The external morphological structure of the human nose varies among different races (Zhu et al. 2011). These differences in nasal index – the ratio between nasal breadth and nasal height multiplied by 100 – are generally characterised into 3 distinct nasal types: lepthorrhine (nasal index below 70), mesorrhine (nasal index of 70 – 85) and platyrrhine (nasal index of above 85). A high index indicates a broad nose; a low index indicates a narrow nose. The lepthorrine, mesorrhine and platyrrhine nasal types are commonly associated with Caucasians, Asians and Africans, respectively (see Fig 6) (Leong & Eccles, 2009). It is thought that these differences reflect differing adaptations to climate with platyrrhine 'broad' noses evolving in warm, humid environments and leptorrhine 'narrow' noses evolving in cooler environments where the incoming air requires more warming (Zhao & Jiang, 2014).

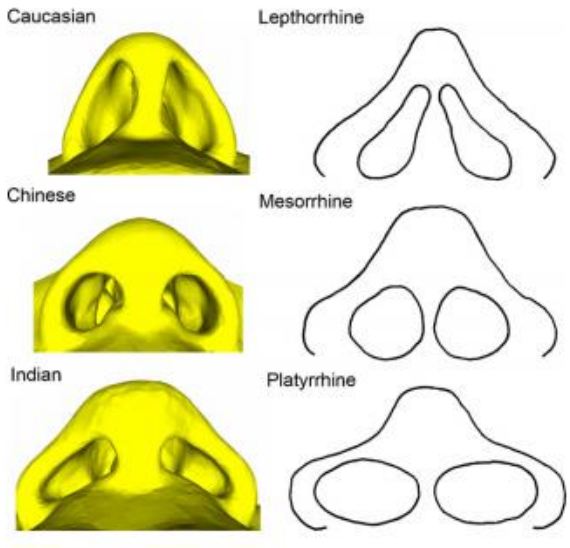

Figure 6: Nostril shapes of lepthorrine, mesorrhine and platyrrhine. Left: nostril shapes from current models (Zhu et al. 2011); right: nostril shapes from Leong and Eccles (2009). Zhu et al. 2011.

Differences in morphological structure of the nasal cavity are hypothesised to correlate with differences in airflow across races. For example, in the Caucasian model, more airflow passes through the middle passage; in the Indian model, more airflow passes through the inferior portion (see Fig. 6). Zhu et al (2011) speculate that "with a longitudinal leptorrhine nostril shape in Caucasian model, it is easy for airflow to reach the middle portion of the passage; while Indian model with platyrrhine nostril, airflow…rarely flows upwards" (p.68).

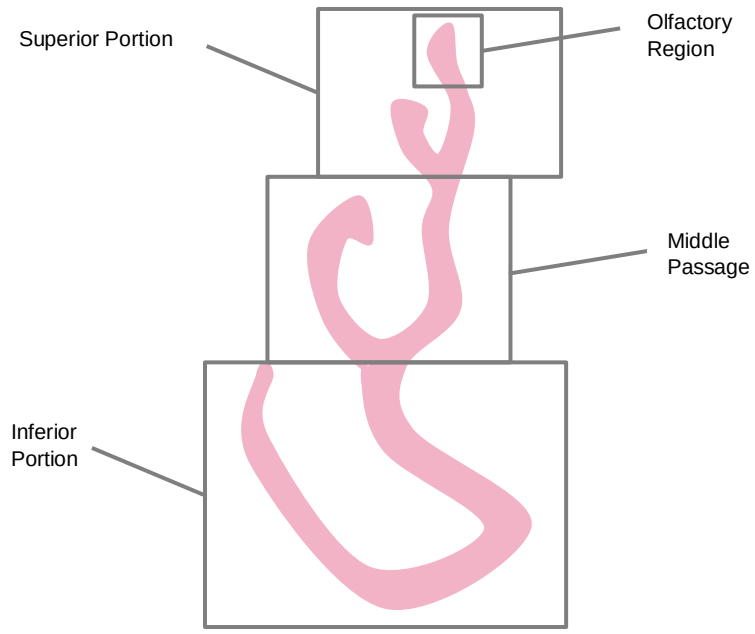

Figure 7: Cross-sectional structure of the nasal cavity.

A certain degree of airflow resistance within the nasal passage is normal and subject to fluctuation during the 'nasal cycle' (Hasegawa & Kern, 1977). Nasal airflow is generally greater in one nostril than in the other due to transient asymmetric nasal passage obstruction caused by erectile tissue; the extent of obstruction alternates across nostrils during the nasal cycle. The functional role of this alternation in nasal airflow is debated in the literature (Kahana-Zweig, Geva-Sagiv, Weissbrod, Secundo, Soroker & Sobel, 2016). Relevant hypotheses suggest that the nasal cycle may work as an 'air conditioning system' and to remove entrapped contaminants (White, Bartley & Nates, 2015), for mucociliary clearance or to protect against respiratory infection or allergies (Eccles, 1996). It is thought that a given nasal airflow may optimise perception of particular odorants (Kahana-Zweig et al. 2016). Interestingly, Indian models demonstrate a lower flow rate in the olfactory region, possibly reflecting smaller velocity magnitude along the olfactory mucus which would make odorants in the air less sensitive to the Indian subject than to Caucasian and African subjects (Zhu et al. 2011).

The literature also illustrates the differences in airflow and aerosol deposition in the nasal cavity of children in comparison to adults. For example, Swift (1991) found deposition of 1 – 10 μm aerosols to be much greater in children than in adults with the same flow rate. Cheng et al. (1995) reported a similar effect in 1.5-, 2.5- and 4-year old children. Such findings suggest that children may be more vulnerable to the effects of air pollution and are therefore more susceptible to respiratory risks than adults.

The underlying mechanisms that allow toxic particulate matter into the CNS and culminate in neurotoxicity remain poorly understood. Multiple potential routes have been proposed; the next section of this report will focus on these.

(1.9.2) Olfactory Pathway

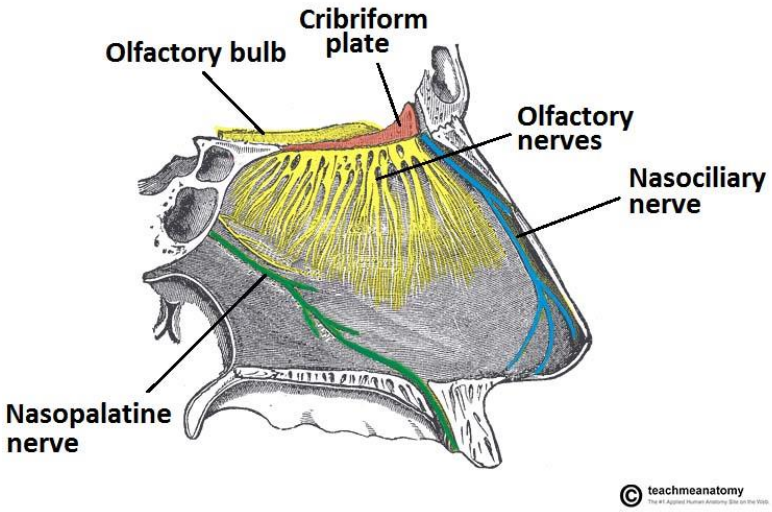

Figure 8: Innervation of the nasal cavity. http://teachmeanatomy.info/head/cranial-nerves/olfactory-cni/ (accessed 02/04/2018)

Calderon-Garciduenas et al. (2004) propose a direct route of entry for AP into the CNS via the olfactory pathway. Axons from olfactory receptors embedded in the mucous membrane of the nasal cavity enter small nerve bundles which project to the olfactory bulb (see Fig. 8) Autopsy studies of the brains of feral dogs exposed to high levels of AP showed a gradient-like distribution of tissue damage and accumulation of metals in this pathway; damage is most severe in olfactory mucosa; then olfactory bulb; and least severe in the frontal cortex (Calderon-Garciduenas et al., 2002). This implicates the nasal pathway as a key portal of entry of AP particles into the CNS. It is possible that particulate matter may be deposited in the epithelial layer of the nose via impaction and cause damage to that layer, eventually penetrating deeper into the olfactory pathway and causing damage at the level of the CNS (Calderon-Garciduenas, Solt, Henríquez-Roldán, Torres-Jardón, Nuse, Herritt et al., 2008). Indeed, children born in Mexico City, which has very high concentrations of O3 and PM, showed breakdown of the epithelial barrier in the nose (Calderon-Garciduenas et al., 2004).

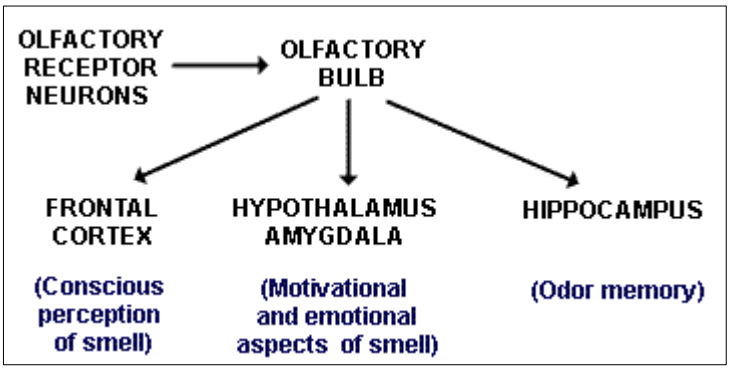

Figure 9: Summary of olfactory pathways (https://faculty.washington.edu/chudler/chems.html, accessed 31/03/18)

(1.9.3) Size Matters

Particulate matter can be deposited in the lungs in a number of ways and the size of these particles partially determines how and where this takes place:

1. *Impaction*: All airborne particulates possess momentum, the product of their mass and velocity. Aerosol particles are much more massive than gas molecules, and so possess much more momentum than the gas molecules surrounding them and travelling at the same speed. Particles with more than a threshold mass will possess enough momentum to remain on a straight trajectory when the gas flow changes direction abruptly, e.g. in the human airway. Such particles will collide with the walls of the respiratory tract. Particles with a diameter of 10 µg or more therefore usually impact in the nose or throat and are deposited there.
2. *Sedimentation*: Particles which enter the respiratory tract settle on the surrounding walls due to the influence of gravity (i.e. during breath holding). This process is relevant to particles measuring between 0.5 and 5ug which are deposited in this way in the surface of the lungs (usually in the bronchi and bronchioles).
3. *Diffusion*: Small particles (0.5ug/^{m3} and smaller) undergo random motion due to molecular bombardment. This movement is known as Brownian motion and is correlated to the size of the particles in question, that is, the smaller the particles, the greater the movement within the fluid (liquid or gas) within which it is suspended (Carvalho, Peters and Williams III, 2011). Over time, Brownian motion causes particles to diffuse down concentration gradients. When random Brownian motion brings a particle into contact with a surface, the particle can be deposited.

(1.9.3) Translocation

A study by Nemmar et al., (2001) provided evidence that the ultrafine particles (particulate matter measuring less than 0.1 µm in diameter) (UFP) can be translocated from the lungs to the extrapulmonary organs (i.e., liver, heart, spleen, brain) via blood circulation. UFP which enters the lungs may penetrate lung tissue and enter circulation via the capillaries where it may then be translocated in circulation to other extrapulmonary organs (Peters, 2006). Once embedded in the lung tissue (via sedimentation or diffusion for example), the mechanism by which PM may penetrate lung tissue is

largely unknown. Shimada (2006) proposes 3 possible mechanisms by which AP in the lung might be translocated into circulation: (1) cell mediated active transportation; (2) passive transportation/diffusion; and (3) active or passive transportation through gaps between alveolar epithelial cells (the 'gap-fenestration pathway'). It is possible that large gaps may appear in the functional pores of the blood-air barrier allowing UFPM to pass through. AP may therefore enter the bloodstream and achieve access to the CNS this way.

However, once circulating in the bloodstream, AP particles must penetrate the blood-brain barrier (BBB) in order to interact with brain tissue itself. The BBB is a highly selective permeable barrier that separates the circulating blood from the brain and extracellular fluid in the CNS. The BBB is formed by brain endothelial cells. Endothelial cells line the interior surface of blood vessels and lymphatic vessels and act as an interface between circulating blood and the rest of the vessel wall; controlling the passage of materials and transit of white blood cells into and out of the blood stream. Weakening of the tight junctions between the cerebral endothelial cells, the choroid plexus epithelial cells and the cells of the arachnoid epithelium in the BBB increases permeability and may jeopardise BBB integrity. This weakening may lead to 'leaks' in the BBB; allowing toxins into the brain where they may cause neuroinflammation and neuronal damage/death (Abbott, Patabendige, Dolman, Yusof, & Begley, 2010). Excessive/prolonged permeability of the endothelial monolayer (caused by such events as chronic inflammation) can lead to tissue edema. It has been suggested that excessive production of proinflammatory cytokines 'activates' endothelial cells and disrupts BBB (Block & Calderón-Garcidueñas, 2009). Chronic inflammation may lead to an increase in levels of circulating cytokines that can cross the BBB and evoke a neuroinflammatory response. It has also been shown that aluminium nanoparticles injure endothelial cells and damage the BBB (Chen & Schwartz, 2008). This could lead to peripheral inflammation and the systemic release of inflammatory mediators which, over time, activate immune surveillance cells and alter CNS immune response, function and behaviour (Block, Elder, Auten, Bilbo, Chen, Chen et al., 2012) (see fig. 6).

(1.9.5) Gastrointestinal Tract

The gastrointestinal tract provides another potential route of entry for AP into the CNS. The 'gut-brain axis' describes the biochemical signalling which occurs between the gastrointestinal tract and

the CNS. Some AP particles are removed from the lungs via mucocillary transport (i.e. via swallowing) and cleared by the gastrointestinal tract. It is possible that AP particles receive gastrointestinal exposure this way and have an adverse effect on health.

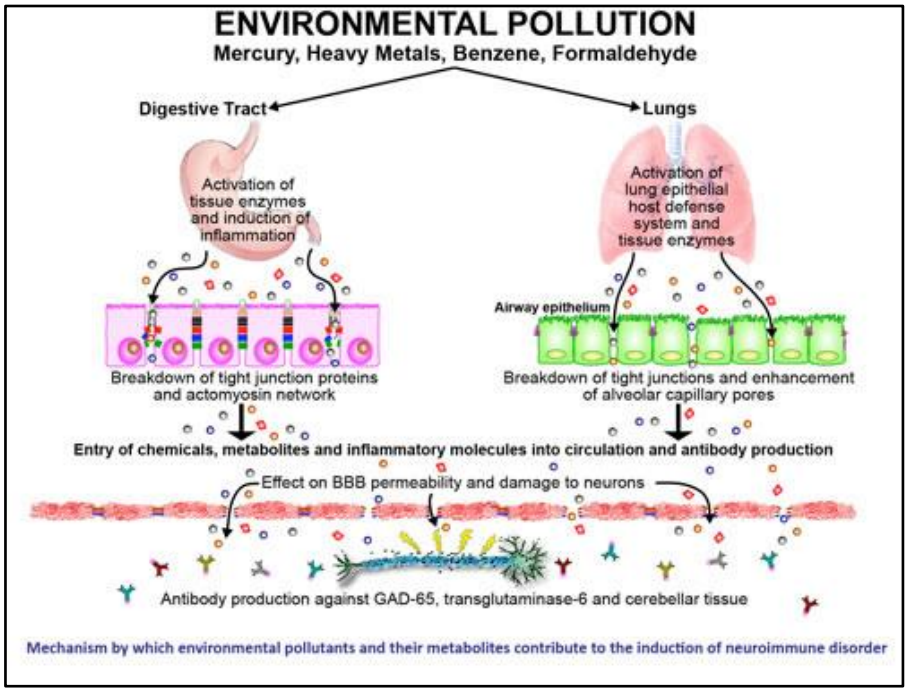

Figure 10: Proposed mechanism for the effect of environmental pollutants on the BBB, leading to neuroautoimmunity (Vojdani, 2014). GAD-65 (glutamate decarboxylase) catalyses the decarboxylation of glutamate to GABA and CO^2. Transglutaminase-6 is involved in the formation of barriers and stable structures within an organism.

Exposure to high levels of air pollution (AP) has been linked to increased risk for Inflammatory Bowel Diseases (IBD) including Ulcerative Colitis and Crohn's Disease (Kaplan, 2010). Indeed, individuals under the age of 23 were significantly more likely to develop Crohn's Disease if they resided in an area high in the gaseous pollutant NO_2 (Kaplan, 2010). It is possible that exposure to PM may incite inflammatory pathways – central in the pathogenesis of IBD. A study by Kish et al. (2013) found histological damage and pro-inflammatory cytokine expression following exposure to Ottawa urban PM10 by gavage (18 µg/g/day) in colitis-prone mice (IL-10-/- model) to be greater than that of wild-type mice. This suggests that PM10 exposure may have a greater inflammatory effect on those with a predisposition towards inflammation-based disease. The authors also found short-term exposure to

PM10 to be linked with increased gut permeability. They speculate that this may be a direct response of PM10 on epithelial cells or a secondary effect due to PM10 effects on immune function. PM10 is thought to contribute to the production of oxygen free radicals leading to oxidative stress in the epithelia. This causes disruptions at tight junctions and leads to increased permeability (Multu, 2011). In the Kish (2013) study, IL10-/- mice also showed increased expression of the pro-inflammatory cytokine IL-17 in the colon following long-term exposure to PM10. IL-17 is associated with autoimmune and inflammatory diseases. The increased IL-17 response in IL-10-/- mice suggests that under conditions of increased susceptibility, exposure to PM10 could trigger and exacerbate the development of inflammatory diseases through increased gut permeability. PM10 also induced changes in microbial composition in WT and IL-10-/- mice; decreased butyrate concentrations were observed. Butyrate is important in colonic epithelial cell metabolism and induction of host defence peptides; decreased butyrate concentration could lead to decreased barrier function and increased susceptibility to inflammation (Kaplan, Hubbard, Korzenik, Sands, Panaccione, Ghosh et al. 2012).

AP particles which enter the gut might also alter the composition of the microbiome. Altered microbiota composition in the gut may lead to the secretion of bacterial molecules such as fatty acids, GABA, 5HT precursors, cytokines and 5HT which can affect brain function (Petra, Panagiotidou Hatziagelaki, Stewart, Conti, P. & Theoharides, 2015). There is also evidence to suggest that signals from the gut can reach the insula, limbic system, prefrontal cortex, amygdala, hippocampus and anterior cingulate cortex (Enders, 2015). There is also some early evidence to suggest that the role of gut flora and gut-derived inflammation may play a role in some specific conditions including anxiety and mood disorders, schizophrenia, autism and Parkinson's disease (Mayer, Tillisch, & Gupta, 2015, and references therein). Interestingly, irritable bowel syndrome sufferers have an above-average incidence of anxiety and depressive disorders, suggesting that persistent micro-inflammations, damaged gut flora or undetected food intolerances may play a role in the pathology of these neurological disorders. If this is the case, microbiota exposure to AP particles which may damage gut flora may be particularly detrimental to the mental health of these individuals.

It has been suggested that particles in the GI tract may be translocated into circulation and then deposited in other organs (Oberdorster, Sharp, Atudorei, Elder, Gelein, Lunts et al. 2002). Indeed, Jani, McCarthy & Florence (1994) found TiO2 (150 – 500 nm diameter) taken in via food to translocate to the

blood and subsequently be taken up by the liver and spleen. This implicates the GI tract as a possible route for AP particles to reach extrapulmonary organs, including the brain.

(1.10) Mechanism of Effect

AP particles may reach the CNS by one, or a combination, of the routes outlined above (or indeed another, unknown route). However, the way in which AP might then exert neurotoxic effects is as yet unknown. The potential mechanisms which might come about from neural AP exposure and their relationship with cognition are outlined in this section.

(1.10.1) Inflammation

Inflammation is the body's innate immune response to invasion by an infectious agent, toxin or physical, chemical or traumatic damage (Abbas & Lichtman, 2009). The detection of such insult results in the production of cytokines. Cytokines are produced by many cell populations, the predominant producers being T-lymphocytes (helper T-cells) and macrophages and play an important role in cell signalling. Their main functions involve the regulation and activation of the immune system; they modulate the balance between humoral and cell-based immune responses and the maturation, growth, and responsiveness of particular cell populations. Cytokines are particularly important in signaling appropriate responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction. Cytokines produced by helper T-cells can generally be functionally divided into Th1 and Th2 cytokines. T-helper 1 (Th1) cytokines drive the type-1 pathway to fight viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. T-helper h2 (TH2) cytokines drive the type-2 pathway and up-regulate antibody production to fight extracellular organisms.

Adverse effects of cytokine production can occur if the positive feedback loop which operates between cytokines T-helper cytokines and macrophages which travel to the site of infection is not regulated. When the immune system is engaged, cytokines signal immune cells (e.g. Th1 and Th2) and macrophages to travel to the site of infection and stimulate them to produce more cytokines to aid

resistance to the infection. Under normal circumstances, the body regulates this feedback loop by controlling the release and proliferation of pro-inflammatory cytokines. However, in some instances, the reaction can become uncontrolled, causing excessive cytokine activation in a single place. The reason for this 'cytokines storm' (Ferrara, Abhyankar & Gilliland, 1993) is not entirely understood but may be caused by an exaggerated response when the immune system encounters a new and/or highly pathogenic invader. Cytokine storms have potential to do significant damage to body tissues and organs (Kärner, Meager, Laan, Maslovskaja, Pihlap, Remm, et al. 2013.). For example, a cytokine storm occurring in the lungs may cause the accumulation of fluids and immune cells which may eventually block the airways. In the brain, adverse effects of cytokines have been also been linked to schizophrenia, major depression, and Alzheimer's disease.

Some research suggests that immune regulation requires homeostasis between Th1 and Th2 activity (Brown, Holian, Pinkerton, Lee, & Cho 2016) and there is also some evidence to suggest that exposure to environmental AP may affect this balance. For example, it is possible that early life exposure to toxins may alter immune responses to asbestos via a shift on inflammatory phenotype which causes individuals to become more susceptible to the inflammatory effects of environmental toxins later in life (Brown et al., 2016). 24-hour and chronic asbestos exposure in rats exposed only to filtered air in utero showed elevated levels of IL-1B and TNF-a (Th1) and of IL-6 and IL-5 (Th2). However, rats first exposed to tobacco smoke showed increases only in Th2 associated production in response to asbestos exposure; Th1-associated cytokine production was reduced. This suggests that in utero exposure to environmental tobacco smoke may cause a shift in inflammatory phenotype and alteration in macrophage activation state, but it is not established whether in utero exposure to other particulate pollution has the same effect.

Microglia are the resident innate immune cells in the CNS and are regulators of neuroinflammation (Block et al., 2012). Microglia are necessary for normal function and act to decrease inflammation caused by infectious agents which enter the brain or cross the blood–brain barrier (BBB), before they damage the sensitive neural tissue. However, excessive and/or chronic activation of microglia can cause the over-production of cytokines and subsequent neurotoxicity. For example, in chronic inflammation, microglia remain activated for an extended period, during which the production of cytokines is sustained longer than usual. This increase in cytokine activity (the so-called 'cytokine storm' [see Tip Box 5]) is thought to contribute to initiation and amplification of neuronal damage

(Gonzalez-Scarano & Baltuch, 1999). Chronic microglial activation can be seen in the brains of patients with neurodegenerative diseases, patients who have suffered ischemic stroke, patients with schizophrenia, and children with ASD (Patterson, 2009).

A connection between excessive microglial activation and AP effects on the CNS is evidenced in the literature. For example, rodents exposed to diesel exhaust show neuroinflammation in brain regions with most microglia (Levesque et al., 2016). This implicates microglia activity in AP response. It is possible that AP activates microglia and may amplify microglial response to proinflammatory stimuli. For example, Kleinman, Araujo, Nel, Sioutas, Campbell, Cong et al. (2008) suggest that increased levels of AP-1 and NF-kB in the brains of rats following 6 hour exposure to UF carbon particles may upregulate the production of pro-inflammatory cytokines. This has previously been linked with plaque formation, dystrophic neurite growth, and excessive tau phosphorylation, as well as altered gene expression. Specific brain regions which contain more microglia may therefore be more susceptible to the damaging effects of AP. Indeed, rats exposed to diesel exhaust for 1-month showed greatest increase in migroglial markers in the midbrain (a region high in microglia) in response to diesel exhaust (Levesque et al., 2011).

Inflammation is also implicated in the development/progression of neurodegenerative disease (Gorelick, 2010). For example, Alzheimer's (AD) diagnosis correlates with acute systemic inflammatory events including an increase in serum TNF-a (Homes, 2009), increased cytokine and chemokine activity and the build-up of beta amyloid plaques (Gorelick, 2010) and increased free radical damage to the corpus callosum (Adult Changes in Thought Study; Montine, Sonnen, Montine, Crane, & Larson, 2012). Subchronic DE exposure correlates with elevated levels of TNF-a in the brains of mice (Levesque et al., 2011). TNF-a is a potent proinflammatory cytokine which is elevated in AD and Parkinson's patients and has a causal role in neurotoxicity. The authors found the Substantia Nigra and midbrain to be particularly vulnerable to these effects, suggesting that AP exposure may differentially affect different brain areas. Furthermore, living in areas with high levels of PM is correlated with markers of neuroinflammation and neuropathology associated with neurodegenerative conditions (Ailshire & Clarke, 2014).

(1.10.2) How Might Inflammation Affect Cognition?

It is possible that inflammation affects cognition by impeding neurogenesis. IL-6 in particular is thought to be a key blockade to neurogenesis (Monje et al., 2003). Prenatal exposure to IL-6 results in decreased neuronal density in the hippocampus of adult rats and is also detrimental to performance on the Morris Water Maze task (Samuelsson, Jennische, Hansson & Holmäng 2006). As performance on the Morris Water Maze task (MWM) is thought to rely heavily on the hippocampus (Oitzl, Van Oers, Schöbitz & de Kloet,1993), these findings suggest that prenatal exposure to IL-6 may reduce cell proliferation and neurogenesis in the hippocampus; reducing performance on spatial learning tasks. Indeed, Monje (2003) reports exposure to lipopolysaccharide (LPS) – a powerful inducer of acute inflammatory response – to result in a 35% reduction in hippocampal neurogenesis.

Findings by Gibertini, Newton, Friedman & Klein (1995) also implicate the hippocampus as a key site of inflammation-related cognitive decline. The results suggest that circulating IL-1B may also affect spatial learning ability. Rats injected with IL-1B showed impaired performance on the Morris Water Maze task in comparison with controls. Furthermore, rats infected with Legionella pneumophila (Lp) – the cause of Legionnaire's disease and Pontiac fever in humans and thought to elevate levels of circulating IL-1B – showed no improvement in Morris Water Maze performance following 2 days of trials. Animals treated with IL-1B antibodies showed improvements in MWM performance after day 1; improvement was maintained at day 7, illustrating retention. IL-6 promotes astrogliogenesis and oligodendrogliogenesis; it is possible that proinflammatory cytokines, especially IL-6, may divert stem cells into the glial programme at the expense of neurogenesis (Monje et al., 2003). Therefore environmental exposure to AP, if inflammatory, may restrict neurogenesis in the hippocampus and reduce spatial learning ability.

Studies in animals have demonstrated that acute activation of pro-inflammatory cytokine signalling in the brain in response to peripheral immune activation is associated with deficits in hippocampal-dependent memory such as contextual fear conditioning (Dantzer et al., 2008). Ekdahl et al. (2003) found 28-days of LPS infusion into the brains of rats to induce an increase in ED1-immunopositve activated microglia in Dentate Subgranular Zone (SGZ) and Hilus in comparison with controls. LPS-induced inflammation was also associated with an 85% reduction in the number of new neurons in the SGZ of the Dentate Gyrus in comparison with controls. They also found inflammation to

cause impairment of hippocampal neurogenesis after electrically induced status epilepticus (brain insult). This suggests that inflammation causes a reduction in basal and continuous formation of new neurons in the intact hippocampus and in neurogenesis in response to insult in mammals.

(1.10.3) Oxidative Stress

Oxidative stress (OS) occurs when there is an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralization by antioxidants. OS is caused by redox imbalance, that is, the production of Reactive Oxygen Species (ROS) which exceed the capacity of the body's antioxidant defence. OS damages cellular proteins, membranes and genes and leads to systemic inflammation.

AP may induce oxidative stress in the lung, leading to systemic inflammation (Guxens & Sunyer Deu, 2012). For example, exposure to nitrogen dioxide contributes to increased HMOX1 gene expression (a pro-oxidative stress response) in the lung (Mirowsky, Dailey & Devlin, 2016). Increasing levels of circulating cytokines could lead to subsequent CNS inflammation (Guxens & Sunyer Deu, 2012). Furthermore, increased lipid peroxidation (a marker for OS) has also been found in rats exposed to unleaded gasoline fumes via inhalation (Kinawy, 2009), suggesting a direct effect of exposure gasoline fumes on the OS response in mammals.

Indirect evidence of the role of OS in the neurotoxic effects of AP is provided by the finding that a significant inverse association between NO2, benzene and mental development in children is only present when maternal intake of fruit and vegetables during the 1st trimester of pregnancy is low (Guxens et al., 2012). This relationship was maintained after adjusting for maternal vitamin D status during pregnancy, breastfeeding status, parental education, age, maternal pre-pregnancy weight and social class. The relationship was not significant when antioxidant consumption was excluded from the model (Guxens et al., 2012). Fruit and vegetables represent a rich source of antioxidants, the frequent consumption of which has been linked with a reduction in oxidative stress (Miller et al. 2005). This implicates OS as a potential mechanism by which prenatal AP exposure may cause impairments in cognitive development and suggests antioxidant consumption may represent a protective factor against the neurotoxic effects of AP by way of reducing oxidative stress.

Therefore, chronic exposure to AP may increase the oxidative stress response within the body (Guxens et al., 2012). Neurodegenerative diseases have been linked with excessive OS response (Kregel & Zhang, 2007). Furthermore, exposure to AP is thought to increase generation of Reactive Oxygen Species (Guxens et al., 2012) and therefore may represent a further risk factor for the development of AD (Moulton & Yang, 2012). Calderon-Garciduenas et al. 2002) found oxidative DNA damage in the frontal cortex of individuals residing in highly polluted areas; the same individuals also displayed markers for AD. This suggests a possible link between AP and AD by means of OS.

(1.10.4) Hormones and Hormone-like Activity

It is possible that AP exposure might also influence hormone activity. Exposure of growing male rats to DE has been linked with changes in reproductive endocrine function and reduced sperm production and activity (Watanabe & Oonuki, 1999). Hormonal events play a central role in the development and function of the CNS. Therefore, it is possible that developmental exposure to endocrine disruptors may give rise to cognitive effects (Hougaard, Jensen, Nordly, Taxvig, Vogel, Saber & Wallin, 2007).

(1.11) Considerations

(1.11.1) The Complexity of 'Air Pollution' as an Independent Variable

As explored above, the term 'air pollution' encompasses a huge mixture of relevant gases and compounds including small oxidant molecules (NO2, O3), volatile organic compounds (including aromatics), and particulates (PM2.5, PM10, UFP), which themselves are composed of many different kinds of mineral acids and semi-volatile organic compounds. Therefore, when defining the independent variable for study, it is necessary that the type of air pollution under investigation be clearly defined and suitably controlled.

(1.11.2) Other Derivatives of Air Pollution Source

One potential confound to concluding that concentrations of AP are the sole contributor to cognitive impairment, is that some AP sources also produce other factors which may influence cognitive functioning. For example, road-traffic is a source of AP which may have an effect of cognitive functioning (Suglia et al., 2008; Wang et al., 2009 etc.); however, road-traffic also produces a large amount of noise which may be detrimental to performance on cognitive tasks. One study which addressed the interaction between NO_2 and PM10 and road-traffic noise on performance on 5 NES tests found independent effects of AP and exposure to transportation noise on cognitive functioning in primary school children (Van Kempen, Fischer, Janssen, Houthuijs, van Kamp, Stansfeld & Cassee, 2012). The significant association between road-traffic noise exposure at school and errors on the Switching Attention Task (SAT) remained associated after adjustment for NO_2 exposure. The authors also report a significant interaction between AP and road-noise at school for reaction times on the SAT. These findings suggest that future research addressing the relationship between AP and cognitive functioning should consider other factors associated with AP source (e.g. road-traffic noise, visual stimulation) which may interact with the results. Long-term effects of exposure to high levels of road-traffic noise – and the potential interaction with AP findings – are also relatively unknown.

Furthermore, it is noteworthy that interventions to modify air pollution levels (introduction of shrubs, trees etc.) are confounded by changes to the visual environment. Measures to establish the potential interaction between AP and 'visual pollution' should therefore be implemented. Indeed there is some existing research which suggests that natural environments may have a restorative effect on cognitive functioning, especially attention functions (Berman, Kross, Krpan, Askren, Burson, Deldin, & Jonides, 2012; Berto, 2005; Kaplan, 1995; and Lauman, Gärling & Stormark, 2003). Therefore, it is possible that cognitive deficits arising from experience of urban environments may be due, at least to some extent, to the increased attentional demands that these environments place on the visual system, and not entirely due to poor air quality. However, Allen (2015) notes improved cognitive performance following exposure to good air quality separate from other components of a 'natural environment' (the experiment was conducted in a lab). This suggests that air quality itself plays a role in cognitive function which is separate from the physical properties of the environment. Therefore, the relationship between cognitive function and the visual environment should be explored alongside the effects of AP.

(1.11.3) Socioeconomic Status

Some previous research has considered the possible confounding effects of socioeconomic status (SES) on the relationship between AP and cognition (Calderon-Garciduenas & Torres-Jardon, 2012; Lundholm et al. 2014, and references therein). Areas of lower SES are often associated with higher levels of AP (i.e. proximity to major roadways, industrial sites etc.). For example, one-standard deviation increases in SES measures have been associated with ≤ 0.47-µg/m3 lower PM2.5 and ≤ 4.20-ppb lower NOx concentrations (Hajat, Diez-Roux, Adar, Auchincloss, Lovasi, O'Neill et al., 2013). Lower SES also shows associations with cognitive function (Shih, Ghosh-Dastidar, Margolis, Slaughter, Jewell, Bird et al., 2011) and autism (King & Bearman 2011). Therefore, the role of SES must be carefully considered and adjusted for in the examination of the relationship between AP and cognitive function.

(1.8.4) Measurement of Air Quality

In order to establish reliably the effect of ambient air quality on cognition and to consider dose-response relationships, accurate measurement of AP is essential. There are a number of challenges associated with measuring ambient AP levels in the external environment. For example, many components of ambient air cannot be collected and stored for later analysis due to high reactivity or absorption onto the surfaces of containers. Furthermore, atmospheric composition is extremely complex, therefore selectively analysing only one or a few components is methodologically challenging. Finally, many components of the atmosphere, particularly those most reactive, occur in very small concentrations; measurement tools must be suitably sensitive.

Therefore, the equipment used to measure air quality must be carefully selected. Fast-response monitoring techniques are able to measure concentrations of components which fluctuate rapidly (e.g. NOx, O_3). Integrated methods are used to measure components which have less spatial variation (e.g. some PM size fractions). Historically, this equipment has been expensive, complex and stationary, creating limitations in collection capability (Snyder, Watkins, Solomon, Thoma, Williams, Hagler et al., 2013). However, a more recent shift in the AP monitoring paradigm has led to the availability of

commercially available, portable systems which allow individuals to monitor the air quality within their own 'microenvironment' (Snyder et al., 2013). Such systems, paired with physiological sensors and location (GPS) information may provide a much more accurate exposure measurement than those calculated by traditional monitoring systems.

(1.11.5) Acute vs. Chronic Exposure

AP-related health effects are linked to the level and duration of exposure (Snyder et al., 2013). Therefore, future research must consider measuring/manipulating/controlling both these variables when accounting for cognitive effects.

It is also necessary to consider the time-frame within which the effects of AP exposure might present themselves and endure. For example, Saber et al. (2006) found little change in tumour necrosis factor (TNF) response to diesel exhaust particle (DEP) exposure within the first 1-6 hours of inhalation of high concentrations of DE (80mg/m3), but that a three-fold elevation was evident after 24 hours. This suggests that TNF may not be important in early-DEP induced inflammation. The same study however, also found IL-6 expression to be highest shortly after DEP exposure (9-11 fold increase within 6 hours of inhalation) and to have declined to a 4-fold increase from baseline after 1 day. This suggests that IL-6 may play a more important role in the immediate inflammatory effects of DEP inhalation than TNF. This finding is consistent with the EEG data from Cruts et al. (2008), which showed a delayed increase in frontal activity in response to DE exposure. Therefore, latency of the production of inflammatory mediators and cognitive outcomes must be considered in future research.

Similarly, if inflammation is to be studied, it should also be considered whether the inflammatory process being measured is acute or chronic. Acute inflammation occurs in response to exposure to infections (bacterial, viral, fungal, and parasitic) and microbial toxins, tissue necrosis: ischemia, trauma, physical or chemical injury, foreign bodies and immune reactions, and typically occurs within minutes/hours of initial exposure. Chronic inflammation however, the response to persistent injury or prolonged exposure to a toxic agent, has an onset of a few days. Therefore, acute exposure to AP at one time point may induce an acute inflammatory reaction and related alterations in cognition and/or behaviour; yet this sort of exposure may not emulate the persistent exposure to AP the occurs in everyday life. Lifetime exposure may indeed be persistent, thus the more relevant mechanism to consider may be the chronic

inflammatory process. Therefore, researchers must be careful that the mechanism they are assuming to be causal for the cognitive effects of AP are reflective of real life exposure (that is, effects of one-time exposure may not reflect real-life effects).

It should also be considered that there may not be a single mechanism which accounts for the cognitive effects of AP exposure but that different mechanisms may come into play at different stages of exposure.

(1.12) Links to Specific Cognitive Functions

(1.12.1) Spatial Working Memory

Working memory refers to 'a system of temporary storage and manipulation of information in the brain, a function critical for a wide range of cognitive operations' (D'Esposito, Detre, Alsop & Shin, 1995; pg. 279). Hippocampal CA1 NMDAr synapses play an essential role in acquisition of spatial memories (Tsien, Huerta & Tonegawa, 1996). Disruption of NMDArs in the hippocampus has been linked to a blockade of synaptic plasticity and also to memory dysfunction, as indexed by the application of NMDAR antagonists which block the induction of long term potentiation (one of the key resources for memory formation) in hippocampal synapses (Collingridge et al. 1983).

One theory for the neuronal basis of the mechanism which integrates information in memory is 'Memory Allocation'. This theory was initially developed in the late 1990s in the lab of Alcino J. Silva and is based on the notion that the brain assigns pieces of learned information to discrete groups of neurons in regions of the brain involved in forming the memory. In these experiments, a crucial role of the CREB (cAMP response element-binding protein**)** gene was established. CREB is thought to encode a protein that regulates expression of other genes needed for memory. Indeed, introducing extra copies of CREB into specific neurons within the mouse amygdala increased the likelihood of those neurons to store a fearful memory fourfold (Davies, Tsui, Flannery, Li, DeLorey & Hoffman, 2004). Similarly, in experiments which have used a protein to deactivate CREB in specific neurons in the amygdala, emotional memory is suppressed (Davies et al. 2004). This provides further evidence that neurons with higher levels of CREB are more likely to be involved in memory storage. Subsequent experiments

found similar effects in the hippocampus and the cortex (Wood, Kaplan, Park, Blanchard, Oliveira, Lombardi et al., 2005).

The mechanism by which CREB increases the likelihood of a particular neuron to store a particular memory is not known. It is possible that higher levels of CREB in any given neuron have increased excitability than those with lower levels and are therefore 'selected' for memory storage (Zhou, Won, Karlsson, Zhou, Rogerson, Balaji, et al. 2009). Indeed, increasing the excitability of particular neurons in the hippocampus in response to a particular stimulus increases the likelihood that those same neurons will fire in response to the stimulus being presented a second time (Zhou et al. 2009). This suggests that excitability plays a key role in the assignment of memories to particular neurons. Furthermore, connections between neurons with high levels of CREB encoding an emotional memory have been shown to be stronger than those cells which had not been altered to produce excess CREB (Zhou et al. 2009).

Memory Allocation theory also posits that when two memories share many of the same neurons, they become linked. Consequently, activation of these neurons during recall of one of the memories triggers the recall of the other. One factor which may influence the storing of memories in overlapping neural populations includes temporal proximity; memories formed within the same day are more likely to share a neural population than those formed weeks apart. In a study by Silva, Golshanti, Khakh et al., it was found that similar CA1 neurons in the hippocampus were activated when mice were exposed to two different chambers but only if initial exposure to the two chambers occurred within 5 hours of one another. When exposure to the two chambers was separated by a period of 7 days, subsequent exposure to chamber 2 did not elicit activation of the same CA1 neurons that were activated during exposure to chamber 1. This suggests that the strengthening of CA1 dependent memories is time-dependent and requires reactivation of the relevant neural population within a 'critical period'.

Although previously thought to be involved solely in the coordination of immune responses, it has since been established that immune system function is pertinent in many fundamental neuronal processes that are critical to learning and memory (Harrison, Doeller, Voon, Burgess & Critchley, 2014). Immune mechanisms are thought to exert a regulatory effect on a number of such processes, including long-term potentiation (LTP), synaptic plasticity and neurogenesis. Consequently, during systemic infection or injury, this regulatory function is disrupted, resulting in acute memory impairments (Harrison

et al. 2014). When inflammation is severe, cognitive impairment may become persistent; if such inflammation becomes chronic, age-related cognitive decline may be accelerated (Weaver, Huang, Harris, Rowe & Seeman, 2002). As such, it is thought that chronic inflammation may influence the rapid progression of neurodegenerative diseases such as Alzheimer's disease (AD).

Both chronic and acute exposure to ambient levels of air pollution have been linked to increases in inflammatory markers and cytokine activity in animals and in humans. For example, post-mortem examination of the brains of feral dogs from Mexico City showed upregulation of COX2 expression (indicative of chronic inflammation and a feature of clinical progression to early Alzheimer's Disease) (Calderon-Garciduenas et al., 2002) and autopsies of the brains of human Mexican subjects also showed an elevation of COX2 mRNA levels, especially in the hippocampus, of individuals who were residents of highly polluted cities (Calderon-Garciduenas et al., 2004).

In rodent models, daily intranasal exposure to particulate matter over 2 weeks in asthmatic mice has been linked with increased expression of pro-inflammatory cytokines (NF-kB and IL-1a) and chronic inflammation (Campbell, Oldham, Becaria, Bondy, Meacher, Sioutas, et al., 2005). 6-month exposure to diesel exhaust has also been linked to increased pro-inflammatory cytokine TNF-a expression in the brains of mice (Levesque et al., 2011). In this study, TNF-a expression was increased in the olfactory bulb, frontal lobe, temporal lobe and midbrain in response to the highest concentration of diesel exhaut (992 µg PM m^{-3}). The midbrain also exhibited increased TNF-a levels at 311 µgPM/m^3, and 100 µgPM/m^3, suggesting a greater sensitivity to the pro-inflammatory effects of exposure to diesel exhaust in this region.

Structures in the Medial Temporal Lobe (MTL) appear to be particularly sensitive to the effects of inflammation. The MTL contains many structures which are critical to memory performance, including the hippocampus and the surrounding hippocampal region which consists of the perirhinal, parahippocampal, and entorhinal neocortical regions. The mechanism underlying the increased sensitivity of these regions to inflammation is not explicitly known; it is possible that these regions contain relatively high receptor and messenger RNA expression for proinflammatory cytokines and are therefore more responsive to elevations in inflammatory markers.

Experimental inflammation induction in humans has been shown to affect acutely spatial working memory performance via its actions on MTL glucose metabolism (Harrison et al. 2014). In this

study, administration of a typhoid vaccination (*Salmonella typhi*) was found to reduce accuracy on an object spatial location task (analogous to the Morris Water Maze task) 4 hours later. The change in object-location accuracy showed significant correlations with activity change in the bilateral parahippocampal and rhinal cortex. The authors suggest therefore, that inflammation may disrupt the relationship between parahippocampal metabolism and subsequent accuracy for object-location encoding. Indeed, further analysis indicated that it was indeed inflammation-induced changes in right parahippocampal glucose metabolism that mediated the effects of inflammation on object-location memory. The authors further suggest that "systemic inflammation may serve as a transient parahippocampal lesion resulting in a discrete impairment in object-location memory" (pg. 591).

These findings have important implications for understanding how chronic inflammation may exacerbate age-related cognitive decline and the risk of neurodegenerative disease. Indeed, the etiology of AD – selective impairment of MTL-dependent memory (e.g. spatial memory) and preservation of procedural memory – is similar to the effects found in studies of experimentally induced inflammation (Harrison et al. 2014). If chronic and/or acute exposure to air pollution causes inflammation in these areas of the brain, it is possible that this could be responsible for similar declines in cognitive function, especially in spatial working memory.

(1.13) Proposed Directions

Current research has focussed mainly on behavioural measurements for establishing a relationship between air quality and cognitive function. However, utilising brain imaging techniques such as EEG would allow investigation into short-term changes in brain activity induced by AP exposure. Currently, there is only one available study, to our knowledge, which uses this technique (Cruts et al., 2008). The results of this study suggested a delayed response in the frontal cortex following 30-minute exposure to 300$\mu g/m^3$ diesel exhaust exposure. A similar paradigm could be used to expose a dose-response relationship between particular concentrations of APs and brain activity.

The development of portable EEG equipment means that the creation of an artificial exposure environment may not be necessary. It may now be possible to take EEG readings from participants whilst in a naturalistic setting. Air monitoring techniques can then be used to establish the constituent

chemicals and particulate matter of the air at the time of testing. This would provide data regarding real-time activity changes in the brain at the time of exposure to normal ambient compositions.

Further research into the long-term effects of chronic AP exposure is also necessary. Such a longitudinal study may look to correlate postcode AP levels with performance on cognitive tasks at multiple time-points over an extended period. Cross-sectional data may also be of use here. Biological data could also be taken at these multiple time-points in order to establish AP exposure-related increases in inflammatory markers in the blood etc.

Research establishing the mechanism(s) by which AP may impact cognitive function is paramount. Previous research has implicated inflammation, oxidative stress, glial activation, endothelial damage and hormone disruption in the progression of AP-induced cognitive effects (see above). Future research should aim to elucidate which (if any) of these mechanisms are detrimental to cognitive outcome.

A more specific and targeted approach should be taken to the aspects 'cognitive function' which may be affected by AP exposure. Assessments of cognitive functioning that have been used previously include: Strategic Management Simulation software (Allen et al., 2015; Satish et al, 2012), Kaufman Brief Intelligence Test (Harris et al., 2015), WRAVMA (Harris et al., 2015), WRAML2 (Harris et al., 2015), SPMSQ (Ailshire & Clarke, 2014), A-TAC (Lauman et al., 2014), NES (van Kempen et al., 2012), NES2 (Chen, 2009) and ASD diagnostic tools. Used in isolation, these assessments do not provide a comprehensive scope of cognitive ability. Therefore, cognitive testing using an extensive battery of assessments would allow better understanding of the mechanisms which may be damaged by AP exposure. Furthermore, to the best of our knowledge, there is no research as yet which looks at the link between AP exposure and mental health (depression, schizophrenia etc.). One study links prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) to be associated with symptoms of anxiety and depression in 6-7 years olds (Perera, Tang, Wang, Vishnevetsky, Zhang, Diaz et al., 2012). Some research has also linked mental health outcomes with systemic inflammation (for an overview, see Miller & Blackwell, 2006); if AP is causal in the inflammatory cascade, it could be considered causal in outcomes which are derived from it. Investigation of the effects of AP on hippocampus-based functions, including spatial navigation and memory, would also be beneficial. Previous research has found the hippocampus to be particularly vulnerable to effects of proinflammatory cytokines, especially IL-iB and

IL-6 (Gibertini et al., 1995; Samuelsson et al., 2006). These effects are manifested in terms of reduced neurogenesis in the hippocampal formation. These studies also show performance on tasks heavily reliant on hippocampal function (e.g. MWM) to be reduced following exposure to these proinflammatory cytokines. Therefore, selecting the most appropriate measures of cognitive function to study is paramount in order to develop a better understanding of how AP exposure might impact the brain.

Another unexplored area of this nascent field is the possibility of reversing damage caused by AP exposure. The consumption of foods rich in antioxidants during pregnancy seems to act as a protective factor against AP-related cognitive impairment (Guxens & Sunyer Deu, 2012), and it also seems that anti-inflammatory treatment can protect from the progression of AD in patients (Ekdahl et al., 2003), but as yet, no evidence of 'recovery' from AP-related damage has been provided. If inflammatory processes are the mechanism driving AP-induced cognitive decline, reduction in exposure to inflammation-inducing stimuli (that is, a reduction in AP exposure) may allow systemic inflammation to be reduced and the system to be repaired. Exploration of this theory would also be valuable.

Furthermore, the establishment of potential vulnerable populations has important implications. The literature suggests that AP exposure in utero may be detrimental to cognitive outcomes (Harris et al., 2015). Furthermore, aging is associated with increased oxidative stress and neuroinflammation (Kregel & Zhang, 2007); AP may enhance these effects. Stress has also been associated with increased AP effects (Steptoe, Hamer & Chida, 2007). Therefore, individuals exposed to high levels of psychosocial stress (low SES etc.) may show greater vulnerability to AP-related damage.

The current study will address the relationship between chronic exposure to ambient levels of air pollution and cognitive functions which rely on regions of the brain which are hypothesised to be vulnerable to its effects. More specifically, exposure to particulate matter with a diameter of less than 2.5μg (PM2.5) and nitrogen dioxide (NO_2) 3-years prior to cognitive testing will be correlated with performance on spatial working memory and transfer learning measures. It is hypothesised that exposure to high levels of PM2.5 and NOx will confer poorer performance on the spatial working memory task and transfer learning task, as indexed by increased error rates and reduced accuracy.

(2) Method

Participants. A total of 46 participants (12 males) took part in the experiment. They were recruited using email and poster campaigns within the University of Birmingham and received payment of £6 or course credit in return for participation. The mean age was 20.73 (*SD* = 3.68). Exclusion criteria included non-native English speakers, residency outside of the UK within the last 3 years (due to reduced availability of pollution data for non-UK postcodes), BMI 30+, diagnosis of mental illness and/or learning disability, diagnosis of an inflammatory disease (e.g. Rheumatoid arthritis, Crohn's disease), and lung damage or lung conditions (including asthma).

Apparatus. The tasks were presented either on a personal laptop computer (HP Pavillion Notebook PC 17-ab200na) with a 17-inch display (and resolution set to 1920 x 1080 pixel) or on a desktop computer (Stone Intel®Core™i5-4570) with a 27-inch display (and resolution set to 1920 x 1080 pixel). Participants were seated at a desk with their gaze centre aligned with the centre of the screen. Head position was ensured to be approximately 50cm away from the screen and was monitored throughout the experiment. All participants were tested individually in a quiet room, with only the researcher present. Participants responded to task instructions using button presses on a standard keyboard; responses were recorded automatically by the computer.

Participants completed 3 cognitive tasks (a transfer learning task, a spatial working memory tasks and an attention networks task) and 3 questionnaires (an air pollution exposure survey, and two mood/affect scales). The Transfer Learning task, the Attention Network Task and the mood and affect scales were run using the software PsychPy2 (Peirce, 2007) and the spatial working memory task (MemoryArena, private communication) was run using bespoke software developed in MATLAB R2016a. Participants gave their responses using key presses on a standard keyboard. Participant responses were recorded automatically by each of the programmes and interfaced to the computer. The air pollution exposure survey was completed in pen and paper form to allow participants to elaborate on their responses if necessary.

General Procedure

All participants first answered sociodemographic questions regarding their age, education level, socioeconomic status, postcodes of the addresses lived in within the last 3 years and exposure to everyday pollutants (e.g. traffic exhaust) using the Mini-Lifetime Exposure to Air Pollution (mLEAP)

survey, developed for the purpose of this study. Participants then completed the Depression Anxiety Stress Scale (DASS), the Positive and Negative Affect Scale (PANAS), Transfer Learning Task (TL), Attention Network Task (ANT), and MemoryArena task (MA). Each task is described briefly, below.

Performance on each of the tasks was correlated with individual residential air pollution exposure over lifetime. Residential air pollution data was gathered from a UK government database (https://uk-air.defra.gov.uk/data/gis-mapping). The annual average concentrations of PM2.5 and NO_2 at participants' home postcodes were further averaged in order to provide a 'Lifetime Exposure' score. The database provided PM2.5 and NOx measurements from the years 2001 and 2002 respectively; 'Lifetime Exposure' values reflect exposure since these dates; i.e., for subjects with a mean age of 20.73, this covers approximately 75% of life. Self-reported measures of exposure to air pollution were also used to improve characterisation of air pollution exposure for each participant.

(2.1) Behavioural Measures

Transfer Learning Task. The TL task measures participants' ability to transfer contingency knowledge from one context to another, similar context. Participants were presented with one of 4 sets of items, each of which had 4 contingency pairs to learn. Initially, participants received feedback on each of their choices so as to aid learning. In Part 1 of the task, participants were presented with a target and learnt that it is paired with 2 visual stimuli (stimulus 1 → target 1; stimulus 2 → target 1). Subsequently, participants learnt that a second target is related to one of these stimuli (stimulus 1 → target 2).

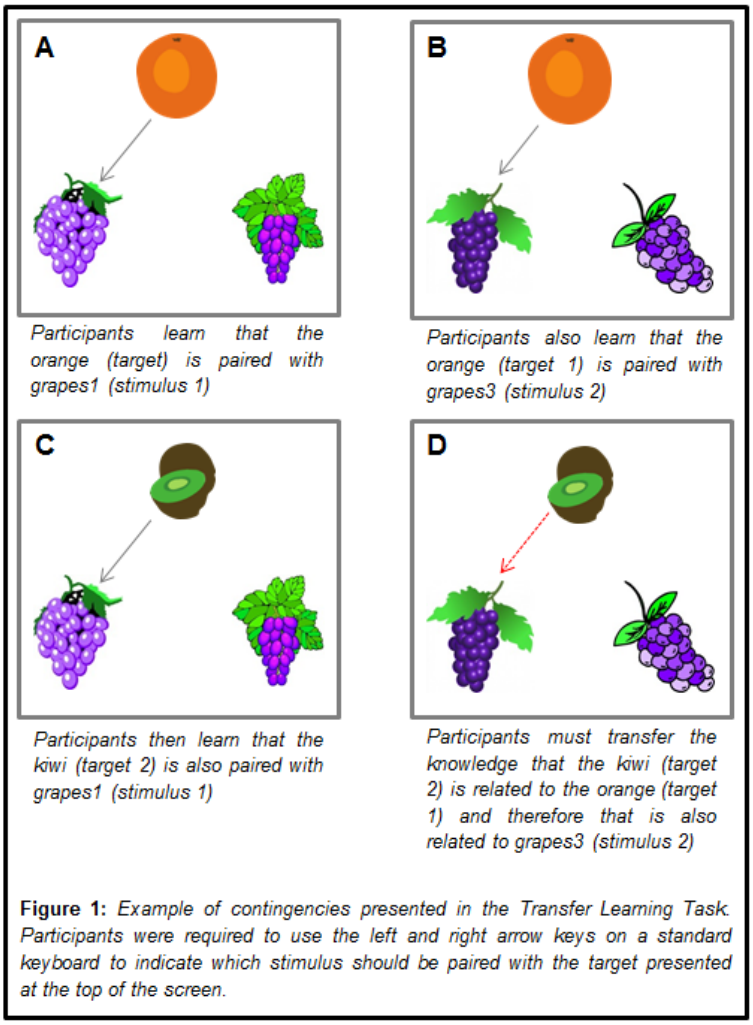

Figure 1: *Example of contingencies presented in the Transfer Learning Task. Participants were required to use the left and right arrow keys on a standard keyboard to indicate which stimulus should be paired with the target presented at the top of the screen.*

In Part 2 of the task, participants are presented with the target and stimuli contingencies presented in Part 1 and responded using the arrow keys. Participants were also presented with a previously unlearnt contingency: stimulus 2 → target 2. Knowledge about the item contingencies learnt in Part 1 must be transferred so as to correctly ascertain that the second stimulus is related the second target. See *Figure 1* for an example. Therefore, Part 2 consisted of both Learned trials (stimulus 1 → target 1, stimulus 2 → target 1, and stimulus 1 → target 2), and Transfer trials (stimulus 2 → target 2).

The target stimulus was presented at [0˚, 4.5˚] and the response stimuli were presented at [-5˚,-4˚] (left stimuli) and [5˚,-4˚] (right stimuli) on a blank screen; monitor-to-eyes distance

approximately 50cm. The stimuli themselves were all approximately 2cm x 3cm in size. All stimuli were presented for 1000ms. Participants were required to use the left and right arrow keys on a standard keyboard to indicate which stimulus should be paired with the target.

Performance was assessed in terms of reaction times (RTs; correct responses only) and accuracy (proportion of correct responses) serving as dependent variables.

Attention Network Task. The ANT was used as a control for attention performance in the TL and MA tasks and as a dependent variable in order to explore whether exposure to air pollution contributed to a deficit in any of the three attentional systems measured in this task (alerting, orienting, executive). The task was based on a modification of the Posner paradigm (Posner, 1980). Spatial priming was used to elicit an exogenous shift of attention to a peripheral cue (↑ or ↓) to which participants would have to respond. The executive feature of the task required participants to respond to the direction of the arrow at the cued location; the cue was flanked by either congruent or incongruent distractors. See *Figure 2*.

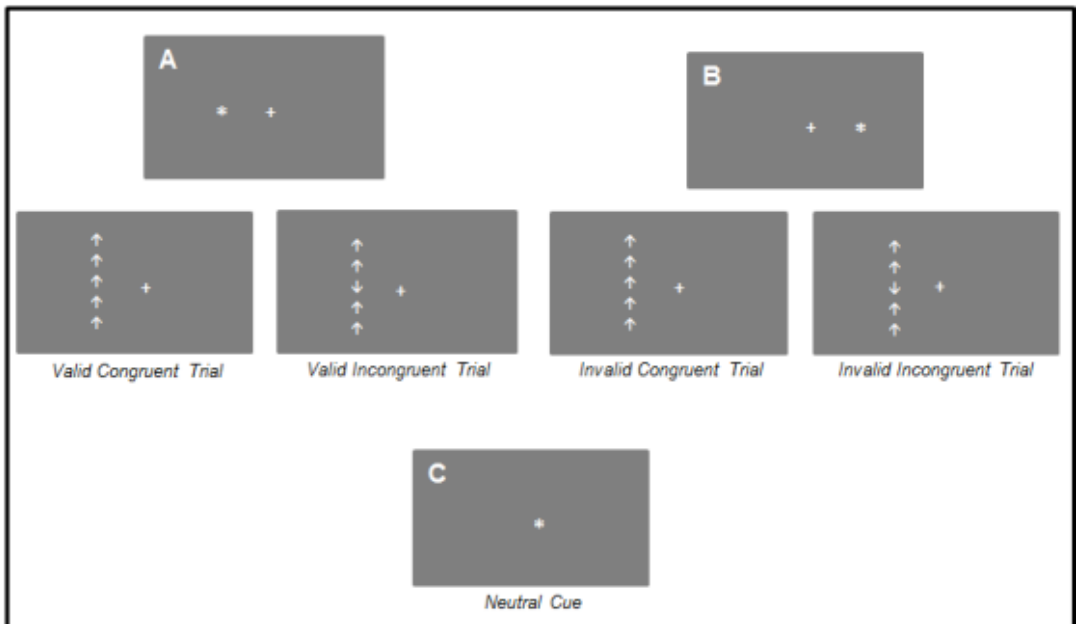

Figure 2: Schematic demonstration of the ANT task with peripheral spatial cues (A + B) and neutral cues (C).

The display consisted of a grey background with a central fixation cross (0˚). Peripheral cues appeared at approximately 7.5˚ of eccentricity in each visual field after 750ms +/- 250ms for 100ms. Targets were presented immediately after fixation for a maximum of 2000ms or until the participant made a response. Participants responded by pressing the arrow key on a standard keyboard which

corresponded to the direction of the target arrow. 80% of the trials were validly cued (target on the same side as the cue); 20% were invalidly cue (target on opposite side as the cue). 50% of the trials were congruent (flanker arrows pointed in the same direction as the target arrow) and 50% were incongruent (flanker arrows pointed in the opposite direction to the target arrow). Performance was assessed in terms of reaction times (RTs; correct responses only) and accuracy (proportion of correct responses) serving as dependent variables.

MemoryArena Task. The MA task is designed to test learning and memory within a spatial paradigm. The task was developed by Professor Ian Charest and Professor Bernhard Staresina at the University of Birmingham (private communication). The background display consists of a circular image ('the arena') which can either be empty, or divided into 4 equal sized segments which are coloured red, blue, yellow and green. In Part 1 of the task (Learning Phase), participants are presented with a series of stimuli (90 pixels in size) which appear at pseudo-random locations within the arena. Stimuli appear one at a time and participants must use the mouse to click on the image in order to progress to the next stimuli (*Figure 3A*). Participants must learn the temporal order of each of the images as well as their spatial positions within the arena. In this version of the task, 12 images of everyday non-emotional items were used. In Part 2 (Training Phase), the stimuli presented in the Learning Phase were arranged around the outside of the arena space and equidistant to one another. Participants had to use the mouse to click and drag the images into the correct spatial location (tolerance for accuracy can be set to 'easy', 'intermediate' or 'hard') within the arena, in the correct

order. Correct responses yielded a positive feedback cue (*Figure 3B*); incorrect responses yielded a negative feedback cue (*Figure 3C*).

The feedback cue remains on the screen for 750m/s. If the participant has entered an incorrect response, the programme automatically carries out the correct movement after 750m/s. Participants are required to reach 80% accuracy on two consecutive trials in order to progress. Part 3 (Test Phase) requires participants to recreate the arena for a final time without receiving any feedback

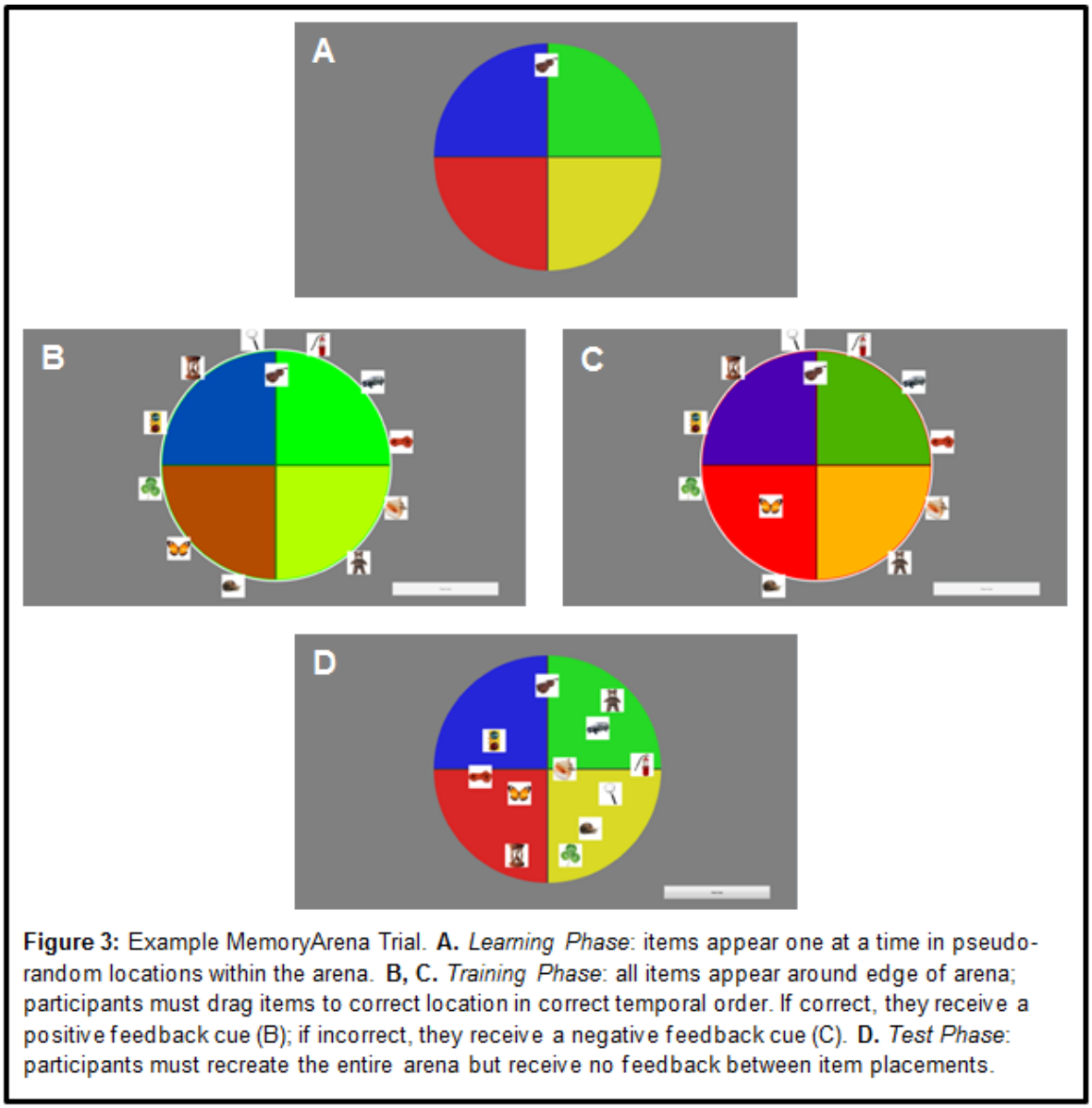

Figure 3: Example MemoryArena Trial. **A.** *Learning Phase*: items appear one at a time in pseudo-random locations within the arena. **B, C.** *Training Phase*: all items appear around edge of arena; participants must drag items to correct location in correct temporal order. If correct, they receive a positive feedback cue (B); if incorrect, they receive a negative feedback cue (C). **D.** *Test Phase*: participants must recreate the entire arena but receive no feedback between item placements.

(*Figure 3D*). Performance measures include the total time taken to complete the Training Phase (achieving 80% correct performance twice in a row), the total number of trials required to complete the Training Phase, the mean and median placement distance of each item in the test phase in relation to

the correct location in the Test Phase, and the mean dragging speed during Training and Test Phases.

(2.2) Self-Report Measures

Lifetime Exposure to Air Pollution Survey (LEAP). The LEAP was designed as part of the current work and aims to obtain information about the levels of exposure to particulate matter and nitrogen oxides that a participant is exposed to on a daily basis and over life to date. Items include 'What is the postcode of your current address?' (to be cross-referenced with measured air pollution data available from a publically available government database), 'How often do you walk or cycle alongside a busy road?' and 'How much time do you spend on an enclosed train platform per week'. The survey was administered in pen and paper form and took approximately 10 minutes to complete.

Depression Anxiety Stress Scale (DASS). The DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. Each of the three DASS scales contains 14 items, divided into subscales of 2-5 items. Subjects are asked to use 4-point severity/frequency scales to rate the extent to which they have identified with each state over the past week (0 – not at all; 3 – all the time). Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. The questionnaire was administered using the software PsychoPy2 and the responses automatically recorded by the computer.

Positive and Negative Affect Schedule (PANAS). PANAS comprises two mood scales, one for assessing positive affect and one for assessing negative affect. Participants are presented with a series of emotional descriptors and must rate the extent to which they have felt these emotions over the past week using a scale from 1 (not at all) to 5 (extremely). The questionnaire was administered using the software PsychoPy2 and the responses automatically recorded by the computer.

(3) Results

(3.1) Air Pollution Exposure

Participants provided the postcodes of their current and previous residential addresses as part of the LEAP survey; postcodes and the dates between which the participant lived at each one were reported. Average annual levels of PM2.5 and NOx at each postcode were determined using the publically available database provided by DEFRA (https://uk-air.defra.gov.uk/data/gis-mapping) and summed to provide 'Lifetime PM2.5 Exposure' and 'Lifetime NOx Exposure' values for each participant. The data was also subcategorized for analysis in order to determine whether a 'critical period' exists for air pollution exposure to have an effect on cognitive performance. '3-year PM2.5 Exposure', '3-year NOx Exposure', '1-year PM2.5 Exposure' and '1-year NOx Exposure' values were calculated in order to explore whether recent air pollution exposure has a greater effect on performance than cumulative (lifetime) exposure. As many of the participants were students at the University, postcode exposure values were also subcategorized into 'Pre-Birmingham PM2.5 Exposure', 'Pre-Birmingham NOx Exposure', 'Post-Arrival to Birmingham PM2.5 Exposure' and 'Post-Arrival to Birmingham NOx Exposure'. Participants' term-time addresses tended to have higher PM2.5 and NOx measurements than their home addresses; it was necessary to explore whether pollution within Birmingham accounts for a significant portion of participants' exposure within the last 3 years. This also allows exploration of whether moving to an area of high pollution has a greater effect on the cognitive performance of individuals with histories of low pollution exposure than those who have previously been exposed to high levels of pollution.

Mean lifetime exposure to PM2.5 within the test sample was 158.88ug/m^3, and to NOx was 517.95ug/m^3. Mean exposure within the last 3 years was 30.66ug/m^3 for PM2.5 and 88.20ug/m^3 for NOx. Further descriptive information is presented in *Table 1* below.

		PM2.5	NOx
Average Lifetime Exposure	Max	307.25ug/m^3	1065ug/m^3
	Min	33.75ugm^3	140ug/m^3
	Mean	158.88ug/m^3	517.95ug/m^3
Average 3-year Exposure	Max	116.38ug/m^3	240ug/m^3
	Min	20ug/m^3	45ug/m^3
	Mean	30.66ug/m^3	88.60ug/m^3
Average 1-year Exposure	Max	24.42ug/m^3	65ug/m^3
	Min	5.63ug/m^3	15ug/m^3
	Mean	10.01ug/m^3	30.70ug/m^3

Table 1: Minimum, maximum and average exposure to PM2.5 and NOx within the sample group

Measures of PM2.5 and NOx exposure were significantly correlated. There were significant correlations between lifetime exposure to PM2.5 and lifetime exposure to NOx (r = 0.686**, p = .000), 3-year Exposure to PM2.5 and 3-year Exposure to NOx (r = 0.715**, p = .000), exposure to PM2.5 prior to moving to Birmingham and exposure to NOx prior to moving to Birmingham (r = 0.737**, p = .000), exposure to PM2.5 since moving to Birmingham and exposure to NOx since moving to Birmingham (r = 0.524**, p = .001) and 1-year Exposure to PM2.5 and 1-year Exposure to NOx (r = 0.417**, p = .005).

A simple linear regression was calculated to predict the total variance accounted for by 3-year Exposure to PM2.5 on Lifetime Exposure to PM2.5. A non-significant regression equation was found (F(1,39)=1.630, p = .209[b]) indicating that 3-year Exposure to PM2.5 did not account for a significant portion of the variance in the Lifetime Exposure measurement. A non-significant regression equation was also found for the relationship between 3-year Exposure to NOx and Lifetime Exposure to NOx (F(1,39) = 2.530, p = .120[b]).

A significant regression equation was found for the relationship between 3-year Exposure to PM2.5 and Exposure to PM2.5 Since Moving to Birmingham (F(1,36) = 8.664, p = .006*[b]), and for 3-year Exposure to NOx and Exposure to NOx Since Moving to Birmingham (F(1,36) = 22.149, p = .000**[b]), indicating that a significant portion of the variance in 3-year Exposure to both pollutants can be accounted for by exposure encountered since moving to Birmingham for the purpose of attending university.

Transfer Learning Task

Total correct responses (%) and RTs (secs) (correct responses only) were the dependent measures included in this analysis. The mean number of correct responses on Learned Trials was 0.764 (*SD* = 0.169) and for Transfer Trials was 0.505 (*SD* = 0.274). Complete descriptive values are reported in *Table 4* below.

	Transfer Task Total Correct	Transfer Task Average RT	Transfer Task Total Learned Trials Correct	Transfer Task Total Transfer Trials Correct	Transfer Task Phase 1	Transfer Task Phase 2	Transfer Task Phase 3
N	45	45	45	45	45	45	45
Range	35.00	2.29	.54	1.00	28.00	20.00	93.00
Minimum	28.00	1.14	.44	0.00	4.00	3.00	15.00
Maximum	63.00	3.43	.98	1.00	32.00	23.00	108.00
Mean	44.5111	1.9845	.7642	.5047	15.6000	6.2667	61.6222
Std. Deviation	10.83056	.51536	.16873	.27381	8.40833	4.79299	34.41147
Variance	117.301	.266	.028	.075	70.700	22.973	1184.149

Table 2: Descriptive information for performance on Transfer Learning measures

No significant association was found between number of correct responses to Transfer Trials and Lifetime Exposure to PM2.5 (r = -0.066, p = .682) or Lifetime Exposure to NOx (r = -0.081, p = .613), nor between Total Correct Responses and Lifetime Exposure to PM2.5 (r = -0.066, p = .691) or Lifetime Exposure to NOx (r = -0.173, p = .281).

Performance on the Phase 1 of the Transfer Learning task – which corresponds to acquiring knowledge of the initial associations between items – was correlated with lifetime exposure to PM2.5 (r = 0.392*, p = .010), lifetime exposure to NOx (r = 0.372*, p = .015) and exposure to NOx in the last 3 years (r = 0.359*, p = .020). No significant associations were found between Phase 2 and 3 performance and any of the exposure measures.

A median split was performed on the data so as to divide participants into a ‘High Exposure History’ group and ‘Low Exposure History’ group, and an Independent Samples T-Test was performed on the data. No significant difference was found between groups for correct responses to transfer items

(%) when grouped by Lifetime Exposure to PM2.5 ($t(43) = -0.232$, $p = .818$), Lifetime Exposure to NOx ($t(43) = 0.845$, $p = .403$), 3-year Exposure to PM2.5 ($t(43) = -0.060$, $p = .953$) or 3-year Exposure to NOx ($t(43) = 0.633$, $p = .530$). However, there was a significant difference between groups in the number of Phase 1 Trials required to learn the initial associations ($t(43) = 3.054$, $p = .005$*).

There was no significant correlation between correct responses to transfer items (%) and BMI ($r = 0.019$, $p = .905$) or other 'Inflammation Confounders' (being on anti-inflammatory medication, having had a bad cold/flu etc.) ($r = -0.076$, $p = .619$).

MemoryArena Task

The descriptive statistics for the dependent variables measured in this task are outlined in *Table 5* below.

	Min	Max	Mean
Number of Training Rounds	2.00	17.00	6.64
Training Duration (Mins)	12	35	18.5
Mean Placement Distance (pixels) (Immediate Test)	20.08	98.63	37.52
Median Placement Distance (pixels) (Immediate Test)	16.53	49.37	33.30
Sequence Preservation (%) (Immediate Test)	41.70	100.00	93.60
Dragging Speed (Immediate Test)	125.00	359.00	241.57

Table 3: Descriptive statistics for MemoryArena dependent variables

There was no significant correlation between Total Number of Training Trials required to reach 80% accuracy and Total Training Duration ($r = -0.027$, $p = .862^{b}$). Dragging Speed was also not significantly related to Training Duration ($r = -0.277$, $p = .073^{b}$). There was no significant relationship between Total Training Duration and Performance on the Immediate Test (%) ($r = 0.147$, $p = .347^{b}$), nor between Total Number of Training Trials and Immediate Test Performance (%) ($r = 0.001$, $p = .996^{b}$).

Lifetime exposure to PM2.5 was significantly correlated with the total number of trials required to learn the correct configuration of items within the MemoryArena ($r = 0.466$*, $p = .002^{b}$). Exposure to PM2.5 within the last 3 years was also significantly correlated with total training trials ($r = 0.430$, $p = .006$*) however, this was mediated when PM2.5 exposure since moving to Birmingham was included in the model ($r = 0.316$, $p = .057$). A linear regression was used to calculate the variance accounted for

by 3-year Exposure to PM2.5. A significant regression equation was found ($F(1,41) = 13.863$, $p = .001$**[b]), with an R^2 of 0.252.

Total training duration was marginally correlated with Lifetime Exposure to NOx ($r = 0.320$*, $p = .044$) but not 3-year Exposure to NOx ($r = 0.286$, $p = .078$), post-arrival at Birmingham Exposure to NOx ($r = 0.319$, $p = .058$) or 1-year Exposure to NOx ($r = -0.087$, $p = .572$).

1-year Exposure to PM2.5 ($r = -0.318$*, $p = .040$[b]), 3-year Exposure to PM2.5 ($r = -0.311$*, $p = .045$) and Lifetime Exposure to PM2.5 ($r = -0.343$*, $p = .044$) were marginally correlated with dragging speed. Average weekly time spent outside was also significantly associated with dragging speed in the testing phase ($r = 0.434$*, $p = .012$).

1-year Exposure to PM2.5 was significantly associated with percentage of correct responses on the immediate test ($r = -0.493$**, $p = .001$).

Time spent outside ($r = 0.399$**, $p = .007$) was significantly correlated with the percentage of correct responses achieved throughout the training section.

Current Smoking Status was significantly correlated with performance (%) on the immediate test (r = -0.299*, $p = .027$), as was Current Smoking Exposure (i.e. living with a smoker) ($r = -0.391$**, $p = .010$). This possible confounding factor was not removed in the regressions reported above.

Attention Network Task

Descriptive information for overall task performance is presented in *Table 6* below.

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Congruent Valid Correct	45	.13	.88	1.00	.9768	.03556
Incongruent Valid Correct	45	.94	.06	1.00	.9213	.18305
Congruent Invalid Correct	45	.25	.75	1.00	.9733	.05996
Incongruent Invalid Correct	45	1.00	0.00	1.00	.9062	.19267

Table 4: Descriptive information for each trial type within the Attention Network Task

There was a significant main effect of cue condition [$F(4,40) = 35.080$, $p = .000$); most efficient performance occurred when an alerting cue was present and when this cue was spatially valid. There

was also a significant main effect of flanker condition [$F(4,40) = 2.841$, p = .007); reaction times were greater when the flanker was incongruent. There was also a significant interaction between cue condition and flanker type [F(4, 40) = 16.915, p = .003]. This is consistent with the design of the test and confirms that the tests were performed correctly.

To analyse median RT data, a 4 (cue condition) x 3 (flanker type) x 2 (exposure history group) ANOVA was conducted. Reaction times (secs) did not differ significantly between participants in the 'High PM2.5 Exposure History' group than the 'Low PM2.5 Exposure History' group [$F(1,43) = 0.531$, $p = .470$[b]]; overall median RT for the 'High' and 'Low' group was 0.340 secs and 0.373 secs respectively. Reaction times also did not differ significantly between participants in the 'High NOx Exposure History' group and the 'Low NOx Exposure History' group [$F(1,43) = 0.331$, $p = .568$]; overall median RT for the 'High' and 'Low' group was 0.343 secs and 0.369 secs respectively.

Performance (% correct) on 'Incongruent Valid' trials was significantly associated with 3-year Exposure to NOx (r = 0.362*, p = .018) and with 1-year Exposure to NOx ($r = 0.330$*, $p = .031$[b]). Performance (% correct) on 'Congruent Invalid' trials was significantly associated with lifetime exposure to PM2.5 (r = 0.491**, p = .001), lifetime exposure to NOx (r = 0.415**, p = .006), exposure to PM2.5 within the last 3 years (r = 0.476**, p = .001) and exposure to NOx within the last 3 years (r = 0.384*, p = .012). Performance (% correct) on 'Incongruent Invalid' trials was significantly associated with lifetime exposure to PM2.5 (r = 0.422**, p = .005) and lifetime exposure to NOx (r = 0.342*, p = .027).

3-year Exposure to PM2.5 and 3-year Exposure to NOx were significantly correlated with Reaction Time (secs) on Congruent Valid trials ($r = 0.552$**, $p = .000$; and $r = 0.500$**, $p = .002$ respectively). Post-Birmingham Exposure to PM2.5 was significantly associated with Reaction Time (secs) on Incongruent Valid trials ($r = 0.337$*, $p = .045$) and Incongruent Invalid trials ($r = 0.340$*, $p = .043$).

(4) Discussion

These results provide evidence that exposure to PM2.5 and NOx may be detrimental to spatial working memory performance. The MemoryArena task was used to measure spatial working memory ability. Performance relies on an ability to encode and recall spatial relational information about a series of items in a fixed temporal order, a process which is thought to rely heavily on the hippocampus (Tsien, Huerta & Tonegawa, 1996). Lifetime Exposure to PM2.5 was significantly positively correlated with the number of training trials required to reach 80% accuracy; participants who had been exposed to higher levels of PM2.5 throughout their lifetime required more training trials to learn the correct configuration of items. This suggests that cumulative PM2.5 exposure may interfere with performance on tasks which rely on hippocampal function. Exposure to PM2.5 within the last 3 years also showed a significant positive correlation with total number of training trials and the multiple regression model found post-arrival at Birmingham exposure to account for a significant portion of the variance for this measure. This suggests that recent exposure to PM2.5 may have a greater influence on this performance measure than cumulative exposure. In terms of NOx, although lifetime exposure to the pollutant showed a significant negative correlation with performance on the task, 3- and 1-year exposure did not, suggesting that cumulative lifetime exposure may exert a greater effect on performance than recent exposure.

Dragging speed was also significantly associated with lifetime exposure to PM2.5 and exposure to PM2.5 within the last 3 years. Dragging speed can be used as a proxy measurement for confidence; slower dragging speed may represent lower confidence in the response being given or in more effortful recall (Robinson, Johnson & Hernden, 1997). It is possible that exposure to higher levels of air pollution interfered with the ability to encode the spatial information required for optimal task performance and resulted in a weaker memory trace in individuals with high exposure histories. This could cause recall of the correct spatial configuration to be more effortful and the confidence in each response to be reduced; slower dragging speed may be a manifest of this effect.

The Attention Network Task was included as a control for attention capacity in the experimental tasks. In healthy individuals, reaction times are normally slower when flankers are incongruent. This reflects the increased time required to resolve the conflict between the target item and flankers (distractors). There is also an interaction between cue and flanker condition; the detriment imposed by

flanker incongruency is enhanced when the cue is non-informative (Gooding, Braun & Struder, 2007). In the current study, performance on 'Incongruent Invalid' trials was significantly associated with lifetime exposure to PM2.5; the normal pattern of performance (poorest performance on Incongruent Invalid trials) is exacerbated in individuals with high PM2.5 exposure histories.

Previous research has found that the apparent effects of inflammation may be related to modulation in psychomotor function, rather than learning/memory ability per se. For example, participants with a greater inflammatory (IL-6) response to a typhoid vaccination (Salmonella typhi capsular polysaccharide vaccine; .025 mg in .5 mL) have been found to have significantly prolonged reaction times on a basic Stroop task (Brydon, Harrison, Walker, Steptoe & Critchley, 2008). This slowing was of the same magnitude for congruent and incongruent trials, despite discrepancies in their respective difficulties. This provides further evidence of an inflammation-induced general psychomotor slowing, rather than a specific deficit for particular tasks. Indeed, the current results did find a significant relationship between Lifetime Exposure to PM2.5 and 3-year Exposure to PM2.5 and dragging speed. This result could reflect a general psychomotor slowing induced by inflammation state.

However, research by Harrison et al. (2014) reported that experimental administration of inflammation via typhoid vaccination impaired accuracy in object-location memory but not in the time taken to relocate objects, illustrating a more specific inflammation-induced deficit. The study also showed no effects of inflammation on a mirror-tracing procedural memory task, providing further evidence that inflammation critically impairs spatial working memory performance and that this effect is not confounded by general decrements in psychomotor responses or motor learning.

Transfer learning performance has previously been linked to individual differences in inflammation state; both humans and rodents have shown reduced transfer learning ability after having been subjected to an environmental stressor which has raised circulating levels of inflammatory markers in the blood (Balter, Hulsken, Aldred, Drayson, Higgs, van Zanten, Raymond & Bosch, 2018). The data from the current study indicated that there was no significant difference between the correct responses to transfer items (%) and lifetime exposure to PM2.5, lifetime exposure to NOx, 3-year exposure to PM2.5 or 3-year exposure to NOx when a median split was used to parse participant's into those with 'High Exposure Histories' and 'Low Exposure Histories'. It is possible that this could be due to a lack of variation in the levels of PM2.5 and NOx exposure in the current sample; the ranges of air pollution

exposure values within the sample were relatively small. For example, average 1-year exposure to PM2.5 had a range of 18.79ug/m^3 (*SD* = 3.61).

Average performance on Learned Trials was significantly greater than on Transfer Trials; average Transfer Trial performance was at chance. However, there was no significant correlation between correct responses to transfer items (%) and BMI or other 'Inflammation Confounders' (such as being on anti-inflammatory medication, having had a bad cold/flu etc.). This finding is contrary to previously reported results (Balter et al. 2018) which have used a similar task. It is possible that homogeneity in inflammation state within the sample group may account for these effects. Participants were excluded if there was the possibility of them currently being in a major inflammation state (e.g. having Inflammatory Bowel Disease or Rheumatoid Arthritis) so as to isolate exposure to air pollution as the most likely factor influencing inflammation state. It is possible that the levels of air pollution to which participants were exposed were not great enough to induce an acute inflammation event; the inflammatory profile of the sample group did not affect performance on Transfer Learning measures.

It is also noteworthy that if exposure to air pollution has a short-term effect on cognition, the levels to which participants were exposed on their journey to the testing room may have influenced their performance. The University is situated within a heavily trafficked area and it is likely that most participants will have commuted along a busy stretch of road on the way to testing. If the levels of pollution exposed to during this period were high enough to induce an acute inflammation event, this could account for the lack of significant difference between the performance of individuals with 'High Exposur55e Histories' and 'Low Exposure Histories'; all participants had a similar baseline level of inflammation when completing the tasks. This could have mediated the effect of cumulative background air pollution exposure. To control for this, providing participants with personal air pollution monitors to wear in the days leading up to the study. This would allow better characterisation of the levels of air pollution participants have been exposed to at the time of testing.

(4.1) Limitations of Experimental Design and Proposed Future Work

A potential limitation of the air pollution measures used in this study is that exposure may not be reliably characterised. Participants were required to provide the postcodes of their previous addresses; this information was inputted into the DEFRA measurement database in order to retrieve

the annual average measurements of PM2.5 and NOx at each location. The DEFRA measurements are provided at 1km spatial resolution; this may not be accurate enough to characterise personal exposure because it will 'smear out' the very strong gradients close to busy roads and in poorly ventilated street canyons. Furthermore, it is likely that participants do not spend the majority of their time at the postcodes given as their 'home addresses'; large amounts of time may be spent commuting or at work and exposures at these locations may be missed. Furthermore, PM2.5 and NOx measurements provided by DEFRA represent outdoor air pollution levels, but it is possible that participants may be exposed to other forms of air pollution within the home (e.g. black carbon from wood-burners, nitrogen dioxide from gas cookers). These exposures were not controlled for in this study and may confound the effects of exposure to PM2.5 and NOx. Furthermore, many more pollutants exist in the external atmosphere than PM2.5 and NOx which may also exert an effect on cognitive performance. PM2.5 and NOx were selected for study in this experiment because they have previously been linked to impairments in cognitive performance when administered in isolation (Cruts et al. 2008), however, this study cannot establish whether it is PM2.5 and NOx exposure alone can account for the effects found. Future studies should use direct administration of pollutants in isolation (akin to the methodology used by Cruts et al. 2008) alongside measures of cognitive performance in order to isolate their effects.

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Appendix

1. Full data set used to create Table 2. (Annual mean concentration of PM10 for 91 countries worldwide, as generated by the World Health Organisation (WHO, 2016), stratified from the highest to lowest figures.)
   https://docs.google.com/spreadsheets/d/1dWYh4xk0G6K3B0R4jSj2TJZQ11ADWPtv15i_Vh0MMeY/pub?hl=en_GB&hl=en_GB&hl=en_GB&output=html