The Impact of Air Pollution on Cognitive Function

by

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Abstract

The impact of air pollution (AP) on cognitive function is widely understudied. Currently, most evidence focuses on correlating chronic AP exposure to performance on off-the-shelf cognitive tests in children and ageing participants. This thesis aimed to investigate the impact of both acute and chronic AP exposure on attention, socio-emotional processing, and episodic memory in clinically health adult populations using specially designed behavioural tasks. Using both experimental and quasi-experimental methods, participants were exposed to AP from a range of sources including Particulate Matter (PM) through candle burning; Traffic-related Air Pollution (TRAP) through quasi-experimental measurements during commuting; and Diesel Exhaust (DE) though the use of an atmosphere chamber. Participants in all studies were clinically healthy adults aged between 18 and 50 with no history of cardiovascular or neurological disease. Results indicated a reduction in pro-social behaviour 24 hours following acute exposure to PM and TRAP and lower cognitive control 4 hours following acute exposure to DE. Critically, no immediate effect of acute AP exposure was identified on these functions. The delay between exposure and cognitive dysfunction is suggestive of inflammatory mechanisms as a likely explanation for the identified effects. An immediate deficit in spatiotemporal encoding ability following acute TRAP exposure was identified, suggestive of hypoxia as a mechanistic explanation. However, no episodic encoding difficulties were identified after PM or DE exposure, nor any effect of any AP species on recall ability. This suggests that episodic memory is preserved despite the identified socio-emotional and executive deficits. Chronic exposure was quantified using participant residential postcodes throughout the lifetime. Higher chronic AP exposure was associated with lower cognitive control, indicative of neurodegeneration or stunted neurodevelopment. Together, the findings highlight an impact of AP on the quality and ease of decision making, emotional control, and learning of new information. These processes are critical to successfully navigate the complex ever-changing human environment, and degradation of these processes could lead to risk-taking, aggression, and degradation of mental health.

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Table of Contents

List of Figures

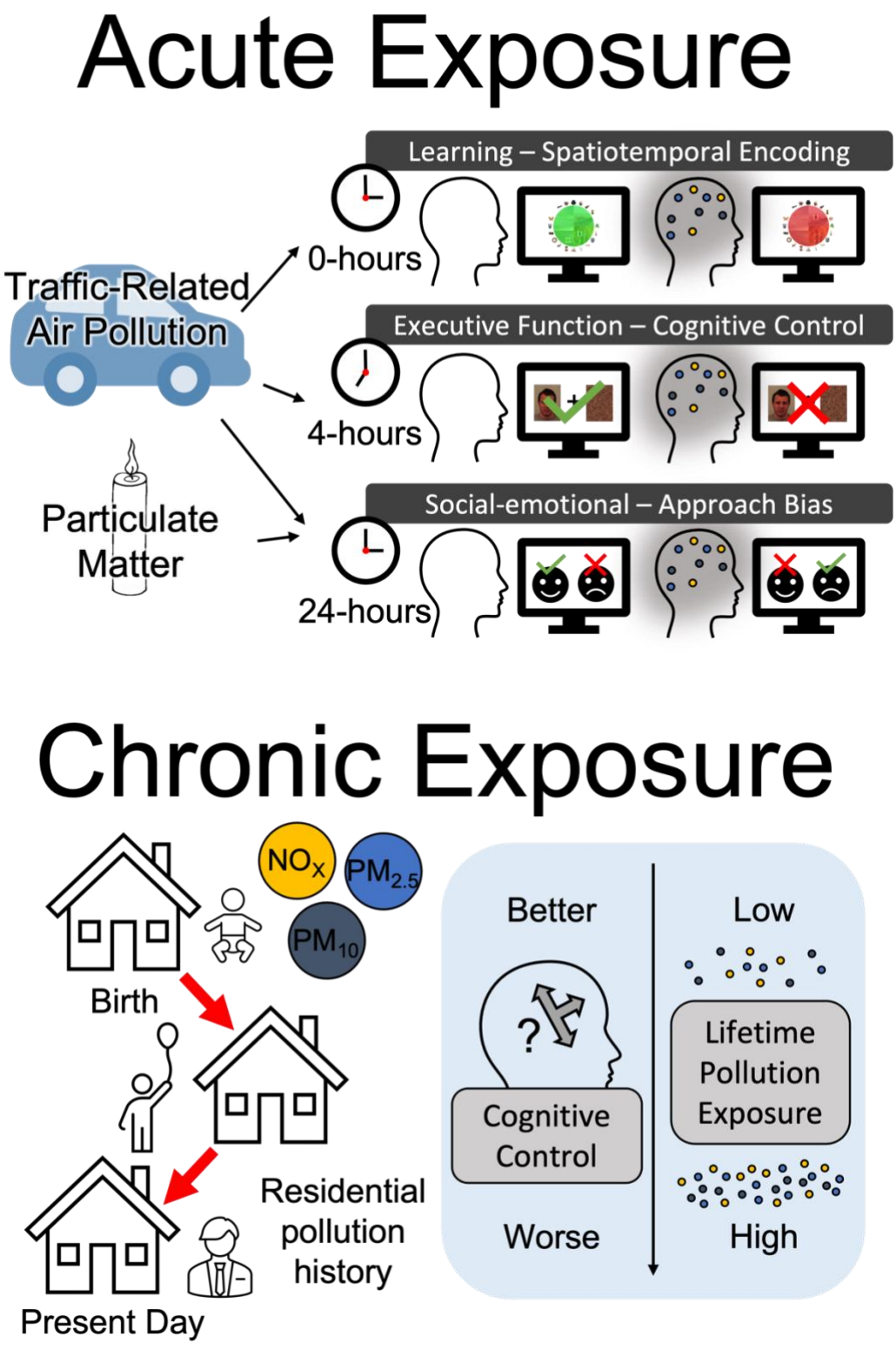
List of Tables

List of acronyms

Acronym	*Definition*
AAP	outdoor (ambient) air pollution
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
AMY	amygdala
ANOVA	analysis of variance
ANT	attention network task
AP	air pollution
ASQ	autism spectrum quotient
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BF	Bayes factor
BMI	body-mass index
BOLD	blood-oxygen-level-dependent
CA	conflict adaptation
CE	congruency effect
CLA	clean air
CNS	central nervous system
CO	carbon monoxide
CO_2	carbon dioxide
COHb	carboyxhaemoglobin
COX	cyclooxygenase
d′	“dee-prime”
DASS	depression, anxiety, and stress scale
DE	diesel exhaust
EC	elemental carbon
EEG	electroencephalography
ERP	event-related potential
FFA	fusiform face area
(f)MRI	(functional) magnetic resonance imaging
FSM	fixed site monitor
GCF	global cognitive function
Hg	mercury
IL	interleukin
iNOS	inducible nitric oxide synthase
IR	infrared radiation
MAC	Manchester aerosol chamber
MATLAB	matrix laboratory
MMP	matrix metalloproteinase
MMSE	mini-mental state examination
NO	nitric oxide
NO_2	nitrogen dioxide
NO_X	nitrogen oxides

Acronym	*Definition*
O_3	ozone
OPC	optical particle counter
OSN	olfactory sensory neuron
PAH	polyaromatic hydrocarbon
PEL	pollution exposure and lifestyle questionnaire
PFC	prefrontal cortex
PM	particulate matter
PM_X	particulate matter with diameter < X μm (With X commonly 10, 2.5, 1, or 0.1)
PNS	peripheral nervous system
PSQI	Pittsburgh sleep quality index
RGB	red-green-blue coordinate
RH	relative humidity
ROS	reactive oxygen species
RT	response time
SO_X	sulphur oxides
TJ	tight junction
TRAP	traffic-related air pollution
VOC	volatile organic compound
WHO	World Health Organisation

Graphical Abstract



Chapter 1 – General Introduction and Literature Review

General Introduction and Literature Review

Air pollution (AP) is prevalent across the globe and adversely affects both cardiopulmonary & respiratory health (Landrigan et al., 2018; Pope and Dockery, 2006), with millions of deaths per year attributable to ambient air pollution exposure worldwide (World Health Organization, 2016). AP exposure has been most thoroughly explored with respect to the risk of developing acute lower respiratory infections, lung cancer, chronic obstructive pulmonary disease, ischaemic heart disease, and stroke (World Health Organization, 2016). More recently, AP exposure has been linked to the onset and progression of neurogenerative diseases, characterised by decline in cognitive functioning due to the death of cortical neurons (Calderón-Garcidueñas et al., 2002). AP exposure has been strongly associated with cognitive decline following inflammation of the brain (neuroinflammation; Levesque and Taetzsch et al., 2011). Whilst the impact of neuroinflammation on cognition has been studied, little research has been conducted into the impact of AP exposure on human cognition, especially over short timescales. It is imperative to assess this considering that human populations worldwide are constantly exposed to pollutants, with more than 90% of the world's population living in regions breaching the 2005 World Health Organization (WHO) air quality standards in 2019 (WHO, 2021a).

To assess the impact of air pollutants on cognitive function, it is important to understand what precisely air pollution is, how it impacts the human brain, and, in turn, the impact of pollutants on human behaviour. This literature review will identify in what environments humans are most exposed to pollutants, use neurobiological evidence to identify which cognitive functions may be most impacted, and, lastly, identify strengths and pitfalls of previous research, motivating future study into the impact of air pollution on cognitive functioning.

Air pollution

What is air pollution?

The major components of the air – four-fifths nitrogen, one-fifth oxygen – is constant throughout the atmosphere for all but the earliest parts of Earth history. Earth's atmospheric composition, in terms of constituents present at trace concentrations (i.e., less than one part in a thousand by volume or mass) changes constantly via a complex system of local and global phenomena (Seinfeld and Pandis, 2016, p. 3-5). Air pollution (AP) is the term for any substance,

or combination of substances, in air that causes harmful effects. Ambient (outdoor) AP causes ~3 million deaths per year worldwide through adverse effects on cardiopulmonary health, leading to chronic obstructive pulmonary disease, ischemic heart disease, lung cancer, and stroke (Pope and Dockery, 2006; WHO, 2016). Ambient AP exposure is also linked to the progression of neurodegenerative diseases such as multiple sclerosis and Alzheimer's disease (Calderón-Garcidueñas et al., 2002), Parkinson's disease (Levesque and Surace et al., 2011), as well as neuropsychological illnesses (Wang et al., 2017).

The main pollutants which cause these health problems are particulate matter (PM) and reactive nitrogen oxides [Nitric oxide (NO) and nitrogen dioxide (NO_2), known collectively as NO_X (NO + NO_2)]. PM is formed of both organic (i.e., carbon-containing) and inorganic compounds such as pollen, soot, ammonium sulphate, and mineral dust. There are different classes of PM based on operational definitions of aerodynamic diameter. Coarse PM refers to particles larger than 2.5 micrometres (μm) in diameter. PM_{10} is a measure of the mass concentration (i.e., mass per unit volume, usually expressed as μg m^{-3}) of particles with aerodynamic diameter smaller than 10 μm. Fine PM refers to particles smaller than 2.5μm in diameter. $PM_{2.5}$ is a measure of the mass concentration of particles with aerodynamic diameter smaller than 2.5 μm. Ultrafine PM refers to particles under 0.1 μm [100 nanometres (nm); United States Environmental Protection Agency, 2021a], although number concentration, as opposed to mass concentration, is most frequently used to describe particles below this size. To give an indication of scale, the average human hair is estimated to be 50 – 70 μm in diameter. (See Figure 1.1).

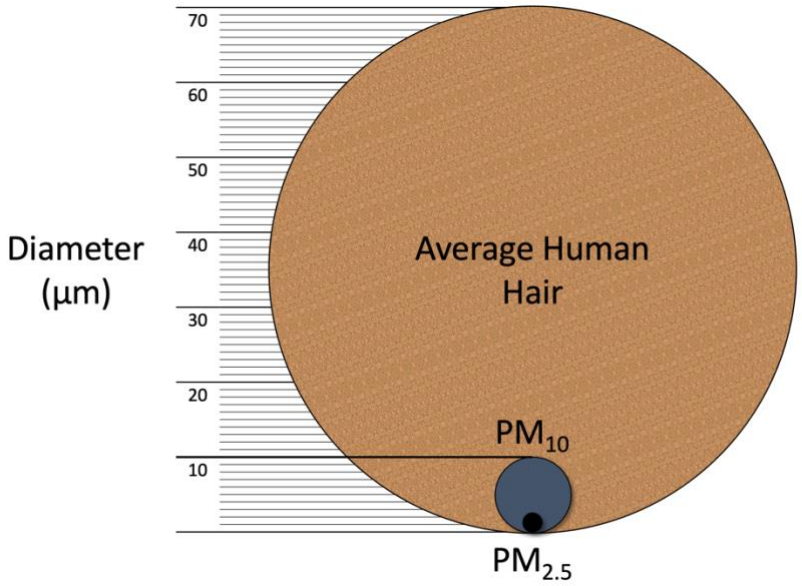
A main reactive nitrogen oxide of epidemiological concern is nitrogen dioxide (NO_2), a gas compound formed from oxygen and nitrogen under high temperature conditions such as in combustion and lightning (United States Environmental Protection Agency, 2021b). NO_2 is a major pollutant with long-established air quality standards and is often the focus of air quality research.

As of September 2021, the highest acceptable mass concentration of average $PM_{2.5}$ identified by the WHO is 5 μg m^{-3} averaged over a year and 15 μg m^{-3} averaged over 24 hours (daily mean). For PM_{10} this value is 15 μg m^{-3} averaged over a year and 45 μg m^{-3} as a daily mean. (WHO, 2021b). Within this thesis, WHO guidelines are defined as the pre-2021 limits (Annual $PM_{2.5}$: 10 μg m^{-3}; daily $PM_{2.5}$: 25 μg m^{-3}; annual PM_{10}: 20 μg m^{-3}; daily PM_{10}: 50 μg m^{-3}; WHO, 2005). In the United Kingdom in 2017, London breached the (pre-2021) daily WHO legal limit of

$PM_{2.5}$ exposure within 5 days (BBC, 2017), with second city Birmingham also showing excessive levels of PM_{10}, $PM_{2.5}$, and NO_2 within the city centre and suburbs (Birmingham City Council, 2016).

Figure 1.1

Relative Size of PM_{10} and $PM_{2.5}$ to the Average Human Hair

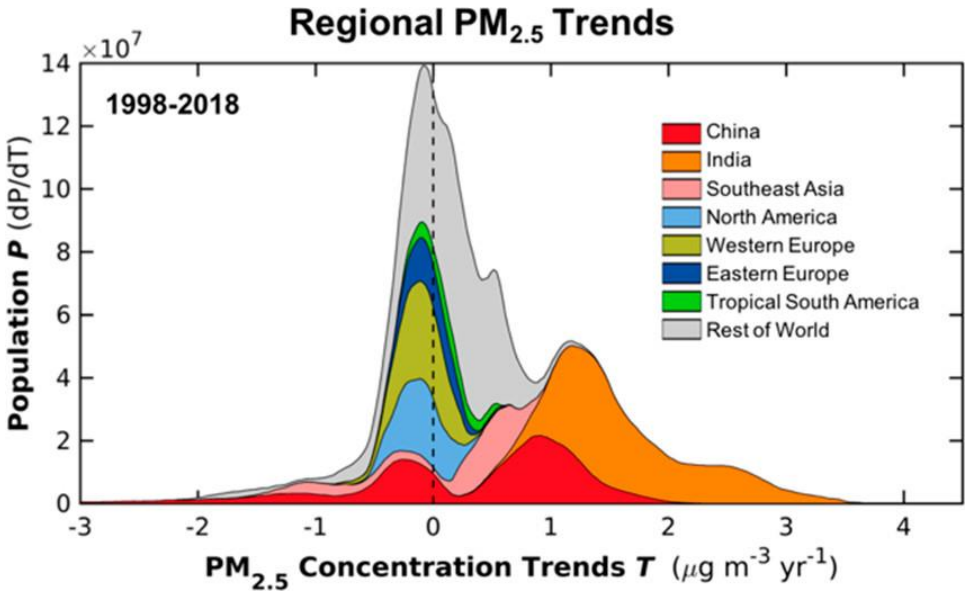


Note. Particles are not uniform in shape (Seinfeld and Pandis, 2016, p. 388)

The extent of these pollutants is growing worldwide due to continued global diesel car use (Schiermeier, 2015), burning of fossil fuels (Figueres et al., 2017), burning of solid fuels such as wood (Bari et al., 2011), and day-to-day activities such as cooking using gas, especially frying and barbecuing (Apte and Salvi, 2016). Whilst recent evidence suggests pollutant levels in Europe and North America show improvements in air quality in recent years, the global trend is a net increase of $PM_{2.5}$ (Hammer et al., 2020). (See Figure 1.2). It is therefore more crucial than ever to understand the mechanisms behind how pollution impacts human health beyond relatively well-known cardiopulmonary effects.

Figure 1.2

Figure from Hammer et al., (2020) highlighting Global $PM_{2.5}$ Concentration Trends from 1998 to 2018



Note. Whilst European and American countries show a decrease in $PM_{2.5}$ concentration over time, as highlighted by distribution peaks (y-values) below 0 on the x-axis, India and China show concentration increases with peaks closer to 1 on the x-axis. Overall, a global increase in $PM_{2.5}$ concentration of 0.04 ± 0.02 μg m^{-3} $year^{-1}$ was reported by Hammer et al., (2020)

Clear distinctions in terminology are necessary to understand the relationship between air pollutant concentration and potential health effects. To clarify, emissions are a certain amount of a pollutant that is released from a specific source within a specified time period; within this thesis, 'emissions' refers to vehicular exhaust. Concentrations are the amount of pollutant matter in the atmosphere per volume unit, most commonly expressed as μg m^{-3}. Exposure relates to human contact with a pollutant concentration, most often expressed as the product (or, more properly, integral) of pollutant concentration and duration. Exposure dose is defined as the pollution mass that the body takes in, with the amount staying in the body denoted by the term 'retained dose'. (Hertel et al., 2016).

For the purposes of this thesis, the assumption is that retained dose is directly related to exposure dose and therefore particle concentrations over time. Therefore, whilst concentrations of pollutants are a key factor, it is necessary to also consider human exposure to pollutants and in turn, the exposure dose, when reporting effects.

Sources of daily air pollution exposure

Pollution exposure and dose are difficult to measure as humans are constantly exposed to sources of pollution within the urban environment, whether it be cooking at home, sitting at an office desk, or walking on the street.

Commuting is a major contributor to personal exposure to pollutants (Rivas et al., 2017) as large numbers of the population engage in highly polluting activities at the same time of day leading to high concentrations of outdoor pollutants for a short time, notably morning and evening rush hours. One transportation method linked to high levels of pollution exposure is driving. A study in Atlanta, Georgia showed that $PM_{2.5}$ levels were twice as high inside vehicles than on the adjacent pavement during rush hour (Vreeland et al., 2017). Recent evidence in Birmingham, UK suggests the opposite may be true, although pollutant levels inside vehicles are directly related to those outside (Matthaios et al., 2020). A review article corroborating findings from multiple European studies highlighted that drivers are more likely to be exposed to higher average Black Carbon, PM_{10}, and $PM_{2.5}$ levels during journeys compared to cyclists (Karanasiou et al., 2014). Interestingly, Goel and Kumar (2015) report that in Guildford, UK, drivers spent only 2% of driving time in pollution 'hot spots', whilst this accounted for 25% of the air pollutants encountered across total drive time, implying that the length of a drive is not necessarily indicative of pollution exposure, but time spent in pollution 'hot spots' may be. This is likely due to traffic levels; pollution inside cars that are stuck in heavy traffic is as much as 40% higher than those in moving traffic (Kumar and Goel, 2016). However, these studies indicated exposure as opposed to dose. Panis et al., (2010) showed that across multiple routes in Belgian cities, bicycle users faced higher dosage of $PM_{2.5}$ and PM_{10} than that of car users, with reference to the fact that cyclists inhaled 4.2 times more per minute compared to drivers on average.

Recent evidence highlights that PM mass itself may not be the most critical factor in determining effects on human health. Source and composition, on the other hand, are salient; urban emissions often have higher oxidative potential (Daellenbach et al., 2020), and whilst currently mixed, there is accumulating evidence that pollution from these sources may increase risk of negative health impacts (Bates et al., 2019). TRAP composition differs between area and is constantly changing based on dynamic factors such as age, maintenance, and fuel type of vehicles. Despite this, it remains a highly ubiquitous AP source in urban areas (Khreis, 2020, p. 7), and with the percentage of global urban population expected to be 68% in 2050 (up from 55% in 2018;

United Nations Department of Economic and Social Affairs, 2019) it will likely remain a pollution source of significant concern. Together, this highlights that road users may be particularly susceptible to the effects of AP exposure given the chemical nature and ubiquity of traffic-related air pollution (TRAP) in urban areas.

Whilst individuals may be subjected to short high-exposure episodes during commuting, pollutant sources are also abundant in the office and the home (Samet et al., 1987) with average PM levels in offices often above legal limits (Nezis et al., 2019) and exposure to other pollutant-species such as volatile organic compounds (VOCs) also of note (Cacho et al., 2013). In the home, one of the major contributors to indoor air pollution is cooking, with one study indicating indoor levels of NO_2 are threefold higher than outdoor levels when cooking with gas (Dockery et al., 1981). Residential air quality is an increased source of concern in lower income countries where fuels such as coal, wood, and charcoal are used for cooking and heating (Lee et al., 2020).

This evidence suggests that humans are exposed to air pollutants constantly throughout the day. Whilst TRAP is of most concern in outdoor urban settings, humans may also experience high-exposure episodes during cooking at home and during work in offices where AP levels are often above legal limits.

Physical factors affecting ambient air pollution concentrations

As ambient air pollution from emissions is identified as a key source in urban regions, it is important to understand how physical factors of the urban landscape may influence dispersal and deposition of AP, directly related to human exposure levels.

TRAP from vehicular emissions are emitted from exhaust pipes close to the road surface. Pollutant concentrations at these expulsion points are very high and there is an exponential decay from the moment they leave the source (Liu et al., 2019). This decay is due to mixing in the air (dilution) and transferral of pollutants from air to surfaces (deposition). Critically, the concentration of pollutants which reach individuals (receptors) is dependent on the environmental pathway taken by pollutants between source and receptor.

Due to the exponential decay of pollutant concentration from emission source to receptor, a larger physical distance between receptor and source allows more time for mixing and dispersion within the air, lowering concentrations when air reaches the receptor compared to a shorter physical source-receptor distance. Similarly, higher windspeed will result in greater dispersion of

pollutants, lowering concentrations at the receptor compared to when windspeeds are lower assuming the source-receptor physical distance is the same (Oke, 1987, p. 315).

Differences in urban form also play a role in dispersion between source and receptor. A stretch of road which includes a narrow street flanked by tall buildings, often described as an urban street canyon, can provide conditions which restrict the dispersion of air pollution, leading to concentration accumulation even in areas with low traffic (Rakowska et al., 2014). Other physical factors may mediate this effect, for example, trees on the pavement in street canyons can induce swirls and eddies which mix pollutants away from the ground, known as ventilation, lowering concentration on the surface. However, again this is dependent on wind speed; evidence suggests that tree-mediated dispersion occurs when wind speeds are higher, therefore reducing pollution concentration, but when windspeed is lower pollution concentration increases as the trees hinder the movement of pollutants in street canyons, known as fumigation (Jeanjean et al., 2016).

Weather is another factor which affects AP concentration. Rain droplets are known to attract and merge (coagulate) with particulate pollution. Coagulated particles are therefore deposited on the ground as rain falls, lowering AP concentrations within the air (Oke, 1987, p. 321; Ardon-Dryer et al., 2015). Sunlight can alter pollutant concentrations through photochemical reactions, for example, NO_X and VOCs combine in the presence of sunlight to form ozone (O_3). Temperature also plays a role in dispersion processes. For example, pollutants may accumulate close to the surface on cool still nights due to inversion, whereby warmer air from higher in the atmosphere acts as a cap to trap the cooler, polluted air close to the surface (Oke, 1987, p. 61).

Complex relationships between weather phenomenon, urban form, and other physical factors mediate pollutant concentration on a small scale, directly related to AP concentrations experienced by an individual, whether physically close to the source or not.

Translocation of pollutants to the brain

Methods of translocation

With pollutants prevalent in breathable air, all pollutant-species can enter the human body through the nose and mouth.

One method is direct translocation into the brain through axonal transport from the nasal cavity (Loane et al., 2013). Assuming particles are smaller than ~200 nanometres in diameter, the

size of olfactory sensory neuron (OSN) axons (Hatt, 2009), then particles could be transported between the nose and olfactory bulb on the other side of the skull via OSNs. (See Figure 1.3). Indeed, research shows that the olfactory neuronal pathway is sufficient for translocating ultrafine particles directly into the central nervous system (CNS) in rats (Elder et al., 2006; Oberdörster et al., 2004).

Pollutants can also pass down the trachea and into the lungs, where particles of smaller mass (≤ 2.5 μg) can be inhaled into the gas-exchange area of the lungs (Miller et al., 1979) and enter the blood stream. Once in the blood, pollutants can be transported throughout the entire body, through even the tightest capillaries (Block et al., 2012), therefore translocating to other organs (Du et al., 2016). Importantly, even if pollutants make their way into the blood stream, they may not pass through the blood-brain barrier, a protective wall separating circulating blood from the brain.

Finally, pollutants can also enter the body through dermal contact, also translocating into the blood stream (Araviiskaia et al., 2019). This depends on the physical condition of the skin, concentration of the pollutant, pollutant-species, and duration of contact (Kampa and Castanas, 2008). The skin itself is negatively impacted because of exposure to air pollutants, most notably Polyaromatic Hydrocarbons (PAH), PM, VOCs, and oxides causing skin irritation, ageing, and cancer (Puri et al., 2017). Whilst dermal contact is a viable route of translocation, this thesis focuses on inhalation through the nose and mouth as the primary translocation methods.

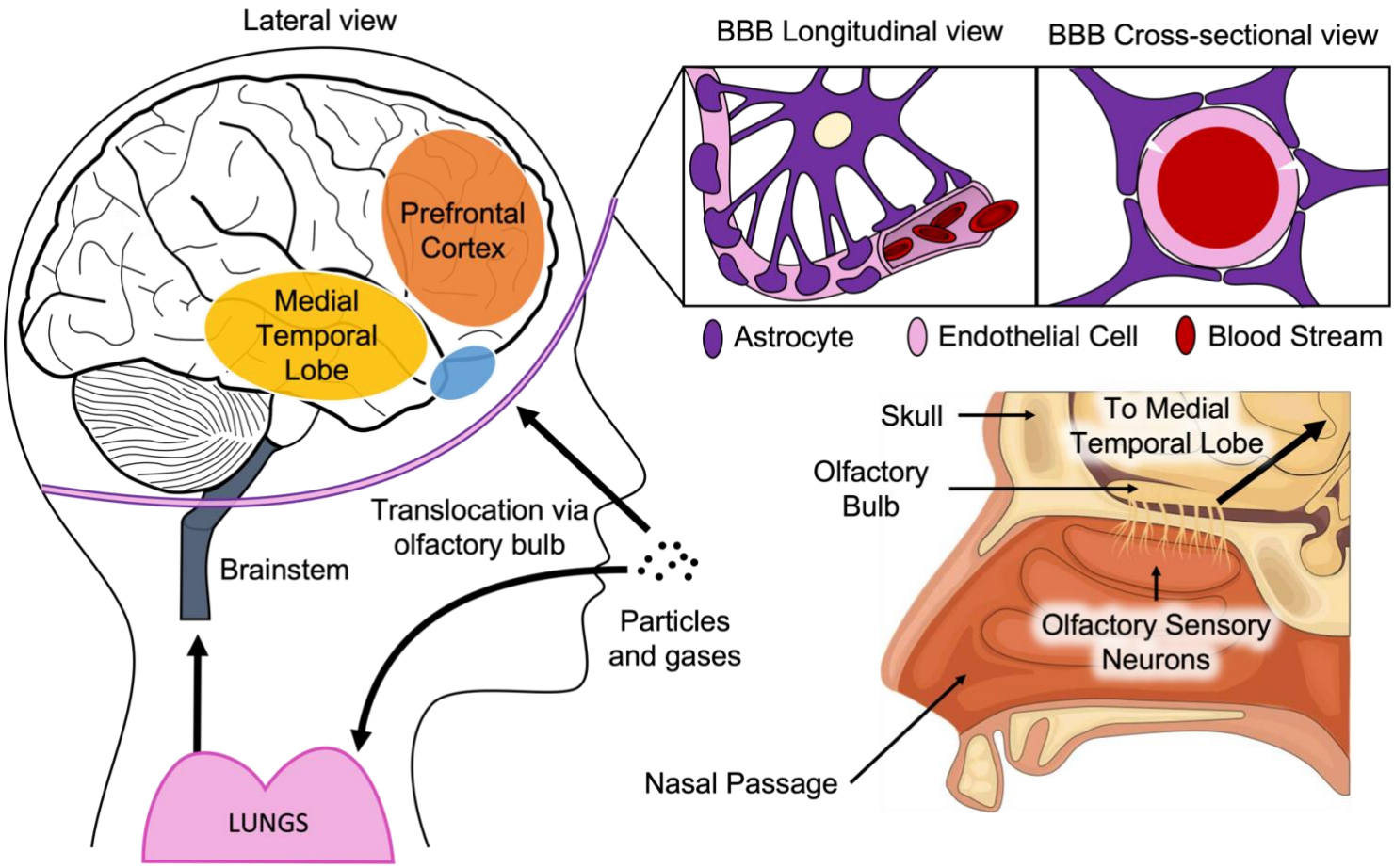
Role of the blood-brain barrier

Unlike the permeable capillary walls throughout the rest of the body, the capillaries in the brain are only semi-permeable to allow lipid-soluble substances to pass through; this is known as the blood-brain barrier (BBB). The barrier is formed from a layer of endothelial cells (single-layer of cells forming the internal blood vessel walls) surrounded by astrocyte (star-shaped glial cells involved in the physical structuring of the brain and maintenance of the BBB) end feet thus constricting the normally permeable pores forming a tight junction (TJ). (See Figure 1.3). The primary role of this barrier is to regulate substances passing through, protecting the brain from those which are harmful, pollutants being a prime example.

The permeability of the BBB is impacted by inflammatory cytokines, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs). The behaviour of these molecules is therefore crucial when investigating translocation of air pollutants into the CNS, to be discussed in full in the next section.

Figure 1.3

The Potential Pathways of Air Pollutants into the Brain



Note. Olfactory bulb diagram (bottom right) adapted from illustration by Alkov (iStock, 2017); this diagram shows the ability of particles and gases to enter the brain directly through the nose via Olfactory Sensory Neurons. Leftmost diagram indicates this pathway as well as particle translocation to the lungs, respiration into the blood stream, and transport to the brain; the blue circle indicates the Olfactory Bulb. Lastly, the top right diagram illustrates the structure of the normal-state blood-brain barrier including the role of astrocyte end feet in preventing translocation through the endothelium in the cross-sectional view

Mechanistic responses to air pollution exposure

Hypoxia

One potential mechanistic response to air pollution dose is hypoxia, a state wherein the brain is starved of oxygen (MacIntyre, 2014). Oxygen is transported to all cells in the body by binding to haemoglobin within the blood. The brain requires oxygenated blood to function normally, as evidenced by blood-oxygen-level-dependent (BOLD) contrasts commonly used in functional Magnetic Resonance Imaging (fMRI) to identify regions of the brain most active at a given time (Vazquez and Noll, 1998). Importantly, other gases can also bind to haemoglobin, prohibiting the transport of oxygen. Most notable of these gases is carbon monoxide (CO), where replacement of oxygen in the blood stream causes tissue hypoxia and can be fatal (Bleecker, 2015). Hypoxia is not only caused by CO induction, but any reduction of oxygen saturation in the body through other means, for example being at altitude where oxygen saturation is low (McMorris et al., 2017). Other air pollutant-species can also bind to haemoglobin, potentially restricting oxygen flow to the brain resulting in mild-hypoxic effects and poorer behavioural functioning as a result. However, note that oxygen is much more prevalent in air than pollutant-species; therefore the concentration of haemoglobin-blinding species would need to be substantially high to cause such effects.

Neuroinflammation

A more involved reactionary mechanism of pollution dose is a CNS inflammation response, often known as neuroinflammation.

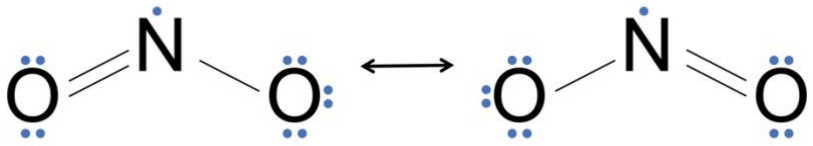
Critical to understanding this response is the role of cytokines. Cytokines within the brain are both produced routinely (constitutive) and are also expressed under conditions of adaptive value (inducible; Erickson et al., 2012). After a toxin is noticed, cells induce cytokines (signals) that travel to other cells which in turn; respond appropriately, often initiating protective mechanisms to remove the toxin, for example, inflammation.

Within the brain, the primary role of pro-inflammatory cytokines such as interlukin-6 (IL-6) is to keep the brain healthy by targeting and expelling unwanted toxins and bacteria which find a way through the BBB. Cytokines also signal the BBB to open and close; cytokine expression is thus both a cause and result of BBB permeability (Yarlagadda et al., 2009).

Reactive Oxygen Species (ROS) are chemicals in which oxygen atoms are incompletely bonded and so retain some free radical behaviour; one example is NO_2, a regulated pollutant species. Importantly, ROS are unstable due to unoccupied spaces in their electron shells, leading them to be highly chemically reactive. Human cells contain antioxidants, which transfer electrons to these reactive molecules to stabilise them. Importantly however, the concentration of ROS within cells can exceed that of antioxidants, leading to what is known as oxidative stress. This imbalance of ROS and antioxidants can cause cell apoptosis (programmed cell death) and even DNA mutations leading to a net loss of neurons (Devasagayam et al., 2004). Increased levels of ROS such as NO_2 may therefore be an important feature to consider when identifying the impact of oxygenated pollutants on cell health and therefore cognition. See Figure 1.4 for the bond structure of NO_2 highlighting the central Nitrogen atom with singular unpaired electron in both cases, which gives NO_2 its free radical status.

Figure 1.4

Two Possible Lewis Structures of NO_2



Beck-Speier et al., (2005) identified that ROS formation is activated by all ultrafine particle types, likely due to reactive metals on some particle surfaces (Leikauf et al., 2020). Research by Lund et al., (2009) similarly suggests that exposure to traffic-generated pollutants result in ROS induction as well as MMP expression in body vasculature. Ansari, (2017) reports that AP exposure leads to higher volumes of ROS within the CNS and therefore poses a clear risk of inflammation and cell death through oxidative stress. Whilst the rise of ROS from PM is not a fully understood process (Kroll et al., 2010), evidence suggests that there is a clear relationship between ROS prevalence and exposure to coarse, fine, and ultrafine PM, and NO_X.

MMPs are enzymes responsible for the degradation of the extracellular matrix. MMPs therefore break down molecules which provide both biochemical and structural support to cells throughout the body (Lee and Murphy, 2004). These biochemical molecules cause disruption of

the BBB through reduction of TJ protein expression, astrocyte loss, swollen end feet, and increased permeability. Collectively, these disruptive processes cause microglial activation, the release of cytokines, and allow entry of toxins and pathogens into the CNS, all of which are constitutive to an inflammatory response of the brain (Ballabh et al., 2004; Obermeier et al., 2013). This inflammatory response may be crucial to understanding the brain's reactive response to air pollution and the effects of this on cognitive function.

Pollution exposure itself is linked to disruption of the BBB. Block and Calderón-Garcidueñas, (2009) identified that chronic exposure to pollutants from vehicular emissions, such as PM, may disrupt BBB integrity. Another study showed an atypically large amount of inducible Nitric oxide synthases (iNOS), enzymes which catalyse the production of nitric oxide in dogs who had been chronically exposed to high levels of air pollution compared to dogs exposed to lower levels. Post-mortem analysis showed alterations of the BBB in the form of degenerated cortical neurons and apoptotic glial white matter cells (Calderón-Garcidueñas et al., 2003). A study using mice showed that exposure to mixed vehicle exhaust, comprising of 100 $\mu g\ m^{-3}$ PM for 6 hours a day, for 30 days, increased the permeability of the BBB. Altered TJ protein expression resulted from increased levels of iNOS, IL-1β, and expression of MMP-9 (Oppenheim et al., 2013). These studies provide strong evidence suggesting that pollutants can impact brain inflammation processes through BBB disruption.

A range of research also finds that air pollution causes neuroinflammation through other processes (Genc et al., 2012). Calderón-Garcidueñas and Solt et al., (2008) showed that high levels of chronic PM exposure (Mexico City residents vs. low-pollution areas in Mexico) resulted in upregulation of IL-1β and another cytokine – cyclooxygenase-2 (COX-2) – in many brain areas including the olfactory bulb and frontal cortex, with COX-2 implicated in neurodegeneration and therefore brain disease (Minghetti, 2004). Disruption of the BBB and increased oxidative stress were also seen in the highly exposed residents, highlighting that exposure to air pollution causes neuroinflammation through multiple processes.

A recent paper highlights the 'neuroinflammation hypothesis' as a strong case for the impact of air pollution on neurodegenerative diseases such as Multiple sclerosis, Alzheimer's disease, and Parkinson's disease (Jayaraj et al., 2017). Put simply, elevation of cytokines and ROS in the brain occurs due to several inhaled pollutants, particularly $PM_{2.5}$ and NO_2. Air pollution inhalation leads to the activation of microglial cells through both direct and indirect processes.

Microglia are a prominent source of both ROS and pro-inflammatory cytokines, implicated in neuronal damage and progressive neurodegenerative diseases (Jayaraj et al., 2017). In another study, 24-hour acute exposure to ultrafine PM led to the expression of neuroprotective proteins, which can be neurotoxic after prolonged induction. This is also linked to longer term genetic changes including an increased susceptibility to neurodegeneration (Solaimani et al., 2017).

Whilst relatively understudied, research suggests that chronic exposure to CO_2 is also related to inflammation and oxidative stress (Jacobson et al., 2019).

These studies indicate that a range of pollutant-species can cause the induction of neuroinflammation. However, this is found following relatively long periods of consistent exposure to high pollution concentrations and may not be representative of an acute response. Despite this, CNS inflammation via cytokine induction may provide a clear framework to understand how air pollution may cause brain inflammation, potentially attenuating neuronal activity, thus altering behaviour.

Systemic inflammation following acute air pollution exposure

Interleukins (IL) are pro-inflammatory cytokines (proteins involved in nervous system inflammation regulation) which are activated in the peripheral nervous system (PNS) when harmful substances such as pollutants or bacteria are identified. Two prominent ILs generated in the PNS are IL-1β and IL-6 (Gabay et al., 2010). These communicate with the brain to induce cytokine synthesis within the CNS (Teeling and Perry, 2009), therefore producing CNS inflammation without direct introduction of pollutants into the brain. This raises the possibility that pollutant induction in the PNS could cause systemic inflammatory effects which lead to an inflammatory response in the brain. Whilst short-term neuroinflammation cannot be directly studied in humans at the present time, a systemic inflammation response can be measured on a relatively short time scale using techniques such as nasal lavage (irrigation), and blood draws. PNS inflammatory responses may therefore provide an indication of CNS inflammation.

To investigate the acute impact of AP on systemic inflammation, one study exposed 15 human participants to Diesel Exhaust [DE (300 $\mu g\ m^{-3}$ PM_{10} concentration)] and clean air for 1-hour in a double-blind crossover design. 6 hours after exposure, a bronchoscopy was performed, and the extracted cells were subject to analyses to quantify expression of several systemic inflammatory biomarkers. Levels of pro-inflammatory cytokine IL-8 were higher after DE

exposure compared to clean air, indicating that a systemic inflammatory response had occurred after 6-hours (Salvi et al., 2000). However, other biomarkers such as TNF-α and IL-1β showed no change. In a similar study, 10 human participants were exposed to DE (200 μg m^{-3} PM_{10}) and clean air for 2 hours also in a crossover paradigm. Evidence of an airway inflammatory response was seen 4 hours after exposure (Nightingale et al., 2000). However, no change was identified between pollution exposure groups for inflammatory biomarkers in the blood.

Another study exposed 18 human participants to DE (300 μg m^{-3} PM_1) for 3 hours. This study utilised 2 exposures to clean air and 2 exposures to DE, with nasal lavage and blood sampling pre-exposure, immediately post-exposure, and 20 hours post-exposure. Whilst no changes were identified immediately post-exposure, induction of inflammatory markers was seen at the 20-hour time point (Xu et al., 2013). This timeline matched that of a similar study by Behndig et al. (2006), who identified increased IL-8 concentrations in bronchial lavage 18 hours post-exposure. One study failed to find any change in four widely studied biomarkers of systemic inflammation during this interval (Cliff et al., 2016).

Whilst the evidence is somewhat mixed, especially regarding the timeline between exposure and an inflammation response, there is a clear indication that short-term exposure to air pollution can induce a systemic inflammatory response — potentially as soon as 4 hours following exposure.

Sickness behaviour

Sickness behaviour refers to a collection of non-specific symptoms such as fever, apathy, hypersomnia, and social withdrawal during acute infective illness experience that results from human response to pathogens (Vollmer-Conna et al., 2004).

The identified inflammatory timelines following acute air pollution exposure are similar to that of studies investigating the impact of cognitive sickness behaviour symptoms following vaccination. Sharpley et al., (2016) identified that typhoid vaccine leads to inflammation as indicated by increased levels of cytokine IL-6 measured two hours post-injection; similarly, Harrison et al., (2015) reported that typhoid vaccination induced 3 times the 'normal' number of cytokines in the CNS four hours post-injection. The use of vaccinations is therefore suggested to be a reliable method for inducing neuroinflammation. However, caution is required using this

paradigm as there may be other impacts of 'sickness behaviour' from vaccinations, e.g., fever, that confound findings.

Memory processing

A range of current research into the impact of neuroinflammation on cognition focuses on hippocampal-dependent memory processes, in particular spatial memory. Spatial memory refers to our memory for spatial information, for example the geographical layout of a city or the interior of a house. The right hippocampus is particularly involved in memory for locations within an environment, and the left focused primarily on context-dependent episodic or autobiographical memory (Burgess et al., 2002).

Hippocampal-dependent processes are affected by neuroinflammation in human participants. Harrison et al., (2014) conducted a study where neuroinflammation was artificially induced via typhoid injection. Participants were split into an early or late inflammation group. The early inflammation group received a typhoid injection at time 0 whereas the late inflammation group received a saline (placebo) injection. Four hours later, participants were given the opposite injection. A virtual reality spatial memory task was administered at time 0, 4, and 8 hours (4 hours after the second injection). Blood assays identified that there was a rise in pro-inflammatory cytokines IL-1 and IL-6 between the first and second test in the early inflammation group, and between the second and third test in the late inflammation group. This timeline was consistent with degradation of spatial memory performance, with a significant difference in performance between task administration 1 and 2 in the early vs. late inflammation group. Object location performance (straight placement distance in virtual metres) improved between trials in the late-inflammation group (learning effect), however the opposite was true for the early-inflammation group. Procedural memory was investigated utilising a mirror tracing task where time to complete the task was the dependent measure; performance improved in both groups between task administration 1 and 2 suggesting no impact of neuroinflammation on procedural memory processing. Similarly, there was no difference between time taken on the spatial memory task or on object identity recall, suggesting that the impact of neuroinflammation via typhoid injection leads to a spatial-specific memory deficit. A great strength of this research was the strict participant recruitment criteria, including: no smokers; no incidence of vaccination in the last 6 months; avoidance of alcohol, caffeine, and high fat meals before testing; and, no sufferers of psychiatric

illness or those taking medication. This exclusion criteria allowed for control over other potential sources of brain inflammation, and the use of blood assays validated the change in inflammation response in participants as due to typhoid vaccination. Future research would therefore benefit from controlling for any other potential causes of neuroinflammation bar air pollution. This could be a useful tool. For example, one could test 'saturation' effects by looking at vaccinating participants who have already received a high dose of air pollution. This, however, will not be introduced in the scope of this PhD thesis.

Reichenberg et al., (2001) utilised endotoxin injection to induce cytokine release in human subjects and identified impairment in both verbal and non-verbal memory functions. Over two sessions, participants were given an endotoxin and saline (placebo) injection in random order and tested on a battery of cognitive tests for memory, executive function, and attention. 3 memory tests were utilised: story recall, where 25 items were learned and were recalled immediately and 30 minutes after learning; figure recall, where an 18-item figure was copied then recalled 3 and 30 minutes later; and lastly, word list learning, where a 15-item list was learned and immediately recalled. There was no difference between groups in executive function or attention measures, however a global decline in all memory functions was identified in the endotoxin group compared to the control. Blood measures were collected at baseline and then hourly after injection identifying an increase of IL-6 between 1 and 2 hours after injection, and an increase of IL-1 between 2 and 4 hours after injection. A problem with the use of an injection of this type is that it can cause strong sickness and mood-based changes in the participant, which may contribute to the cognitive changes identified. Despite the researchers' using a low dosage, one deemed not to produce these sickness-based mood changes, significantly higher depressive and anxiety symptoms were reported by participants after endotoxin injection compared to the control. As in Harrison et al., (2014), the sample was heavily controlled for, including identifying any abnormalities in blood and urine tests prior to participant recruitment. This study provides a clear timeline of cytokine increase following sickness-induced inflammation, which may be applicable to cytokine release following pollution exposure. However, it could take a longer time for pollution to reach the blood compared to vaccination paradigms, in which the inflammatory agent reaches the blood almost immediately. The study also serves as a reminder that vaccinations may produce mood or other changes that could act as confounding variables when assessing the impact of neuroinflammation on behaviour, which are necessary to avoid.

Attention and social-emotional cognition

As well as hippocampal-dependent cognitive deficits associated with neuroinflammation, there is also evidence to suggest an impact of neuroinflammation on both social cognition and attentional processing. There is a suggested link between brain inflammation and major depression (Moieni et al., 2015), a psychopathy that includes social-cognitive deficits as a symptom. Following this, Balter et al., (2018), conducted a study into the impact of neuroinflammation on social cognition. Importantly, typhoid vaccination in clinically normal participants elicited a short-term inflammatory response without symptoms of physical sickness or mood changes. The study showed that inflammation via typhoid injection resulted in a deficit in performance on Baron-Cohen's 'eyes task' six hours later. In the task participants are shown emotionally expressive faces with only the eyes visible and choose an appropriate emotional label to match the expression (Baron-Cohen et al., 2001a). Recently vaccinated participants were less able to correctly identify the emotional state of another person by looking at images of their eyes. This provides novel information into the impact of neuroinflammation on social cognition, which warrants further investigation.

Balter et al., (2019) conducted a follow-up study investigating the impact of typhoid vaccination (or placebo) on the Attention Network Task (ANT) coupled with non-invasive brain imaging [electroencephalography (EEG)]. Heightened inflammation levels were observed 6 hours following injection, as measured by IL-6 levels. Despite no changes identified in performance on the ANT, there were significant differences in EEG activity between the vaccination and placebo groups. Task-related changes in brain activity were observed indicating that oscillatory alpha band activity was correlated with inflammation levels, indicating that those injected with the typhoid vaccine needed to exert more cognitive effort than those in the placebo group to perform similarly on the task. The results suggest that inflammation may underpin attentional functions, although differences in EEG measures related to executive function were not identified.

Inflammatory timeline

The timeline associated between exposure and identified deficits is necessary to understand the cognitive implications of neuroinflammation. Törnqvist et al., (2007) suggest that systemic inflammation, measured as IL-6 cytokine expression and blood plasma oxidation, persists for up

to 24 hours after inhalation of Diesel Exhaust for 1 hour. This is a plausible explanation for the observed increase in acute cardiovascular events 24 hours after a peak in traffic-related PM air pollution. This study clearly highlights the extensive impact that mixed pollutants have on pro-inflammatory cytokine IL-6, and the persistence of inflammatory biomarkers in the body after exposure events.

Human microglia exposed to 2 $\mu g\ ml^{-1}$ ultrafine particles showed an increase in pro-inflammatory biomarker TNF-α and a decrease in ROS formation. This decrease in ROS contrasts findings from previous research conducted using rodent cells, suggesting human microglial cells may be more protective than that of rodents to the formation of ROS (Campbell et al., 2014). This finding suggests that the human brain may be more resilient to the impact of air pollution than that of rodents, casting doubt over the suitability of rodent research to inform toxicity assessments. Investigation into human participants is crucial to determine the true impact of air pollution on cognition.

Cognitive effect of chronic pollution exposure

Neurodegeneration and ageing

Lifetime exposure to high air pollution concentrations has been linked to greater risk of progressive neurodegenerative diseases associated with substantial cognitive deficits, such as Alzheimer's Disease (Peters et al., 2019), Parkinson's Disease (Kasdagli et al., 2019), and Multiple Sclerosis (Noorimotlagh et al., 2020). A large body of evidence links air pollution exposure to cognitive decline and dementia (Delgado-Saborit et al., 2021).

As well as an association between air pollution exposure and the onset of neurodegenerative disease, a range of studies have identified relationships between lifetime exposure to air pollution and a range of cognitive deficits.

In Los Angeles, USA, older adults chronically exposed to higher $PM_{2.5}$ concentrations showed lower scores on a verbal learning task; exposure to NO_2 was associated with lower logical memory; and, high O_3 (a ROS) exposure was associated with lower executive function (Gatto et al., 2014). Although the study used strict recruitment criteria, the measure of pollution came from historical data from central sites close to the participants' addresses. It stands to reason that the performance on tasks could be related to other factors related to the location of residency rather

than lower quality air, such as socio-economic status, not controlled for in the study. The study used a battery of 14 cognitive tests. None of the pollutants studied were significantly associated with global cognition score, raising the possibility that the use of all-encompassing cognitive testing may not sufficiently sensitive and that targeted cognitive testing when investigating changes in cognition due to air pollution exposure may be required. The use of a battery of tests also has implications for statistical power, as statistical corrections applied lower the α threshold for a significant result, limiting the benefits of non-targeted cognitive testing.

A London-based study conducted by Tonne et al., (2014) used a sample of 2,867 civil servants with residences within the boundary of the M25, London's orbital motorway. Data from a 2002-2004 and 2007-2009 medical examination were compared to modelled traffic-based PM_{10} and $PM_{2.5}$ concentrations, and the same measures from all sources. The medical examination included verbal & mathematical reasoning (Alice Heim – 4I) tests, a 20-item short-term verbal memory recall, and semantic and phonetic fluency. Lower scores on both the reasoning and memory tasks were associated with higher levels of all particle types from all sources when controlled for covariates such as blood pressure, stroke incidence, depressive symptoms, and heart disease. The study, however, did not exclude participants with a history of neurodegenerative disease despite the average cohort age being 66 years old. Contrastingly a strength of the study was that participants all worked in central London civil service offices, suggesting their working pollution exposure was similar. The large sample size also allowed for high statistical power, although the results should be treated with caution as the majority of participants were old, retired, Caucasian men.

Another study utilised data from a US cohort (Health and Retirement Study) aged 50 and over. Residential concentrations of ambient air pollution ($PM_{2.5}$ & PM_{1}) were modelled for all participants who lived up to 60 km from monitoring sites. Data analysis (multiple regression) controlled for smoking status, socio-economic status, and demographic factors such as gender. A cognitive measure, similar to the mini-mental state examination [MMSE (a test to measure basic global cognitive ability)] was conducted over the phone for 28% of participants and at participant residences for those remaining. Results of the test were used to create two distinct factor scores: Episodic Memory and Mental Status. Higher chronic PM exposure negatively impacted episodic memory scores although other functions remained intact (Ailshire and Crimmins, 2014).

Neurodevelopment

The cognitive impact of AP exposure has also been studied with relation to neurodevelopment. With evidence linking AP to neuroinflammation (Brockmeyer and D'Angiulli, 2016) and altered neurodevelopment (Calderón-Garcidueñas and Mora-Tiscareño et al., 2008).

Ambient NO_X concentrations in two schools in China were compared to performance on 9 cognitive tests. Average NO_X concentrations were significantly lower outside one school (7 $\mu g\ m^{-3}$) compared to the other (36 $\mu g\ m^{-3}$). Children in the high-exposure school performed significantly worse on a visual simple reaction time and digit symbol task amongst other measures (Wang et al., 2009). This indicated an association between high NO_X concentration and psychomotor slowing as well as visual perception dysfunction. Importantly, confounding factors such as socioeconomic status were controlled for in the analysis.

One study measured TRAP [NO_2, Elemental Carbon (EC), and ultrafine particle number] concentrations both indoor and outdoor for 39 schools in Barcelona, Spain. The *n*-back and attentional network test (ANT) were administered to measure working memory and executive function respectively. Once controlling for confounding variables, it was shown that children from highly polluted schools (both indoor and outdoor) showed less improved performance across test administrations of both tasks compared to schools with cleaner air (Sunyer et al., 2015). This result indicates that working memory and executive function processing is also impacted by air pollution exposure in children.

This pattern of results is replicated amongst a range of studies with child participants with working memory (Delgado-Saborit et al., 2019; Rivas et al., 2019; Basagaña et al., 2016; Forns et al., 2017), executive function (Calderón-Garcidueñas et al., 2011; Gui et al., 2020; Harris et al., 2016), and attention (Sunyer et al., 2017) all negatively impacted as a result of air pollution exposure.

Cognitive effect of acute pollution exposure

Whilst the current literature investigating the impact of acute exposure episodes on cognitive function is sparse, some critical findings are highlighted below in detail.

Behavioural measures

In a study conducted by Bos et al., (2013), participants were split into an urban and rural aerobic exercise group and undertook a Stroop task (Stroop, 1935; testing executive control, inhibition, and task switching) before and after exercise. Concentrations of Ultrafine PM were significantly higher in the urban compared to rural group. Reaction times on the Stroop task improved significantly for the rural group after exercise, whereas this did not improve for the urban group. This suggested that the inhalation of ultrafine particles impaired processing improvements in participants exposed to urban air during exercise. Other tests of cognition including an operation span test (working memory), and psychomotor vigilance test (sustained attention and reaction time) showed no changes. A substantial flaw in this study's methodology was that it did not control for smokers, as smoking heavily impacts brain inflammation levels (Lee et al., 2012). This study indicates that after short-term exposure to high concentrations of ambient air pollution participants show deficits in inhibitory control.

Whilst not an experimental study, Saenen et al., (2016) compared repeated performance on a number of tests measuring selective and sustained attention, short-term memory, and visual processing speed. $PM_{2.5}$ and PM_{10} were measured on each testing day within the school where children were tested as well as recent (within 2 days) measures at their residential home. An association was found between selective attention and visual processing speed and classroom $PM_{2.5}$ exposure with task performance decreasing as $PM_{2.5}$ concentration increased. This implied that exposure to $PM_{2.5}$ reduced selective attention ability and decreased visual processing speed based on daily pollutant measures. Interestingly, chronic ambient exposure to PM was also measured and was also associated with selective attention, but not visual processing speed. This may indicate that some cognitive functions are impacted by both acute and chronic exposure changes whilst others remain intact.

To test the immediate impact of PM exposure on Global Cognitive Functioning (GCF), Shehab and Pope (2019) exposed participants to a burning candle or ambient air (no candle) for one hour before taking part in the MMSE, a sustained and selective attention task, and Stroop task. Global cognitive performance (MMSE) was found to be significantly lower following candle burning than after ambient air exposure. However, no significant differences were identified in the other tasks. Whilst this suggests an immediate reduction in cognitive performance, the MMSE is a clinical measure and may not be valid in the context of this study due to repeated test

administration over a short time period (Gluhm et al, 2013). Interestingly, the response inhibition effect identified in Bos et al., (2013) was not seen here. This difference may be explained by an increase in dosage in the Bos et al., (2013) study due to the use of exercise (and thus participants' deeper inhalation). Differences in composition of naturally occurring ambient PM and PM from candle burning could also explain this.

Using data from a previous longitudinal study (Veterans Affairs Normative Aging Study), Gao et al., (2021) identified an association between score on the MMSE and modelled $PM_{2.5}$ data on the day of testing. This was also compared to a GCF measure consisting of performance on a word list memory task, digit span backwards test, verbal fluency test, and drawings test, although no significant associations were found. Importantly, participant reports of anti-inflammatory medication use mediated MMSE performance, such that anti-inflammatory users were less affected by the adverse impacts of short-term PM levels on cognitive performance than non-users. In line with previous research within this review, it suggests that inflammation may cause reductions in cognitive performance. However, there was no information on dosage of anti-inflammatory medications or reasons why these may have been taken, limiting the conclusions that can be drawn from this study.

Brain activity measures

A different method of assessing cognitive function is utilising non-invasive brain imaging methods such as electroencephalography (EEG), where electrodes are placed onto the scalp to measure the electrical activity of the surface layer of the brain.

Crüts et al., (2008) recorded resting-state EEG measures while exposing participants to either Diesel Exhaust [300 $\mu g\ m^{-3}$ PM; 1.6 parts per million (ppm) NO_2; 4.5 ppm NO; and 7.5 ppm CO] or filtered air (sham condition) in a sealed chamber for 1 hour, followed by a further 1 hour outside of the chamber. The cortical areas under investigation were frontal central, and parietal. Results showed an increase in fast wave activity (20-32 Hz, denoted β2) over the two-hour study period in the four frontal sites in the DE group compared to the sham group, indicating an increase in cognitive processing within frontal brain regions. The prefrontal cortex (PFC) is a key brain area for executive function processing and the results of this study indicate that executive function is critical to investigate in future research. Unfortunately, a serious limitation of this study is that the smell of diesel was obvious to participants, allowing them to easily discriminate between the

sham and diesel condition, potentially impacting EEG measures. This may have been due to the high concentration of DE used in the study considering the annual WHO limit for $PM_{2.5}$ is 25 μg m^{-3} compared to 300 μg m^{-3} reported in this study. This may also restrict the implications of the findings as these concentrations are far higher than experienced on typical city streets.

Following on from this, a study conducted by Driessen et al., (2012) exposed human volunteers to short-term nanoparticle-rich diesel engine exhaust (100 μg m^{-3} PM; 82,756 # cm^{-3} PM; 236 ppb NO_X; and 119 ppb CO) for 1 hour and subjected participants to a 15-word recall test and information processing speed test. Results of the study similarly indicated changes in frontal lobe fast-wave activity, however there was no impact on cognitive performance on either cognitive test identified. What is of note is that the effect of diesel emissions on fast-wave brain (β2) activity was maximal after 4 hours, suggesting a time delay in the onset of brain wave changes from exposure to diesel exhaust. A reason for the lack of cognitive effects identified could have been the tasks used. A more suitable measure in future research would be executive function tests — those related to frontal brain region activation — such as inhibition control.

A more recent study measured frontal-lobe activity on 10 clinically healthy adults during controlled cooking indoors. Participants fried ground beef in sunflower oil using an electric stove in a non-ventilated room. EEG activity was measured pre-, immediately post-, and 30 minutes post-frying. Whilst the peak of AP concentrations was observed immediately post-cooking, slow wave (Δ-band) activity decreased and fast wave (β2) activity increased 30 minutes after exposure (Naseri et al., 2019). Whilst the pattern of activation differed slightly from the previous studies, this may suggest source-specific changes to cognitive functions following pollutant exposure.

Together this evidence suggests that acute exposure to air pollution from multiple sources alters brain function, especially in frontal brain regions. Administering cognitive tasks reliant on frontal brain processes and taking delayed responses into account are therefore imperative in future research.

Other factors to consider

Given the ubiquity of AP in outdoor and indoor environments, the literature that investigates effects of acute air pollution exposure must be careful to identify possible confounding factors clearly and robustly. Without a strong focus on this, it will be impossible to separate experimental effects from others occurring due to this ubiquity.

Firstly, it is known that there is an age-related decline in cognitive processing (Deary et al., 2009). Similarly, Franceschi et al., (2007) suggests that in humans, part of normal healthy aging can be explained by an imbalance of pro- and anti-inflammatory networks, coined as 'inflammaging'. A worse-performing pro-inflammatory response and efficient anti-inflammatory network work in tandem to allow for exposure to damaging agents into the CNS. This suggests that age is an important factor to consider when conducting between-participant comparisons.

Another factor impacting 'resting state' inflammation is body weight. A study conducted by Miller and Spencer, (2014) highlights the link between obesity and cognitive decline in humans. Cognitive decline in obesity can be strongly linked to neuroinflammation, particularly inflammation of the hypothalamus. This hypothalamic inflammation in turn mediates a neurodegeneration response in the hippocampus and other brain areas associated with basic cognitive functioning. Controlling for participant weight may therefore be crucial for research into the impacts of neuroinflammation on cognition.

Interestingly, recent research investigates the impact of genetics on susceptibility of individuals to the impact of air pollution. Children who are carriers of apolipoprotein E, allele 4 (APOE-4), a gene variant involved in the immune response, show associations between nitrogen dioxide levels and attentional problems — with patterns similar for elemental carbon levels. Children who were not carriers of this allele showed no associations between pollutant levels and behavioural problems, suggesting that genetics may play a role in susceptibility, or risk of being cognitively or developmentally impacted by air pollutants (Alemany et al., 2018). Research also showed an interaction between a genetic variant of IL-1β, rs16944m and NO_2 exposure in Parkinson's Disease susceptibility, the mechanisms for which are very similar to that of cognitive deficit following air pollution exposure (Lee et al., 2016). Whilst this is not something which will be investigated within this PhD thesis, it may be an important factor providing additional clarity of results if studied alongside cognitive measures.

Summary

Humans are constantly exposed to varying degrees of air pollution whether at work, commuting, or at home. Particularly acute exposure can occur when close to strong emission sources, as happens when commuting, when cooking (especially frying) with gas, and when in candle-lit rooms. Exposure to $PM_{0.1}$, $PM_{2.5}$, PM_{10}, and NO_X all impact the human brain through

multiple processes, with strong evidence that neuroinflammation plays a central role. This inflammatory response has been related to changes in neurodevelopment, long-term cognitive decline due to neurodegeneration, and even short-term cognitive dysfunction after acute episodes of high concentration exposure.

At present, the majority of research has utilised off-the-shelf cognitive tests such as the MMSE, which may not be appropriate for non-clinical populations (Gluhm et al, 2013), or a battery of simple cognitive tasks which may not be sensitive or specific enough to tease out particular cognitive effects. This review has explored the neurobiological response to the inhalation of air pollutants, and the impact of this neuroinflammatory response on cognitive function. By utilising specified cognitive tasks across memory, social cognition, and executive function domains, future research can investigate the impact of air pollution on cognitive function.

The majority of previous research into the impact of air pollution on cognition uses a wide-range of techniques either to study natural levels of pollutants or induce an inflammation response through vaccination paradigms. Neuroinflammation is caused by many factors; sickness, obesity, and smoking are all linked to increased levels of pro-inflammatory cytokines in the CNS. It is therefore crucial that any further research controls for the effect of alternative pro-inflammatory factors, highlighting the importance of monitoring participant temperature, mood, and other factors which mediate inflammation in the investigation. Similarly, other mechanisms as well as inflammation may cause cognitive deficits.

Another problem with most research on this topic is the use of fixed-site monitors (FSMs) or historical data to gauge personal pollution levels. These measurements cannot give either the spatial or temporal specific needed to adequately measure acute AP exposure especially considering that even small changes in distance and timeframe can correspond to significant changes in pollutant concentration. It cannot therefore be assumed that everyone living within a certain radius of an air monitor experience the same level of pollution.

Future research should avoid the use of fixed-site or historical measurements in assessing acute pollution exposure, and instead use personal measurements in real time. Another reason for tightly controlled pollution measurement is conflicting evidence related to the timeline between exposure dose and behavioural dysfunction.

Future research must use a combination of behavioural measures, fieldwork, and control for non-pollution based confounding variables. It must also carefully select cognitive tasks when

assessing personal exposure to air pollution and that ensure pollution exposure is controlled or personally measured to ensure optimum validity.

Questions to be addressed

Literature investigating the impact of air pollution on cognitive function is sparse. This literature review highlights both inconsistencies between research and raises questions left unaddressed at the present time.

This thesis aims to address the following five questions:

1. What is the impact of air pollution exposure on a clinically healthy adult population?
2. What is the impact of *acute* air pollution exposure on cognitive function?
3. Which cognitive domains are impacted following pollution exposure: attention, executive function, learning and memory, or social cognition?
4. How long following exposure are cognitive changes identifiable, and are these the same across domains?
5. What are the potential mechanisms underlying any identified cognitive effects?

General methods

Multiple experimental procedures were used within this thesis to address the main questions identified above.

A range of computer tasks were used to identify cognitive abilities spanning across multiple cognitive domains. Tasks measured attention, executive function, learning and memory, and social-emotional processing. See Table 1.1 for a summary of all cognitive tasks and their associated measures.

A range of study designs and air pollution exposure methods were used to assess changes in cognition across different pollutant species, exposure durations, and length between exposure and cognitive testing. See Table 1.2 for a summary of each empirical chapter methodology.

By combining multiple experimental methodologies, exposure paradigms, and behavioural tasks across multiple cognitive domains, this thesis aims to identify the impact of air pollution exposure on cognitive functioning in clinically healthy adults.

Table 1.1

Cognitive Task Summary

Task Name	Chapter(s)	Description	Cognitive Domains	Does air pollution impact:
Emotional Discrimination Task	2 & 3	Go/No-go task with emotion expression as classifier	Attention	Speed of response (Psychomotor function)
			Executive Function	Decision making ability (Inhibitory control)
			Social-Emotional	Emotion expression sensitivity (Approach bias)
Memory Arena & Memory Task	2 & 3 4	Spatiotemporal episodic memory for image stimuli	Learning & Memory	Learning new information (Encoding) & Remembering previously learned information (Recall)
Face Identification Task	4 & 5	Selective attention task with emotional face stimuli	Attention	Concentration (Sustained attention)
			Executive Function	Strategic attention modulation (Cognitive control)
			Social-Emotional	Perception of emotion expression (Feature processing)
Flanker Task	5	Selective attention task with non-social stimuli	Attention	Concentration (Sustained attention)
			Executive Function	Strategic attention modulation (Conflict adaptation)

Table 1.2

Experimental Chapter Method Summary

Chapter	Exposure duration	Pollutant species	Experiment type	Study Design	Duration between exposure and testing
2	Acute (~60 mins)	Particulate Matter	Experimental	Mixed	0 and 24 hours
3	Acute (~30 mins)	Traffic-Related Air Pollution (TRAP) *	Natural	Mixed	0 and 24 hours
4	Acute (60 mins)	TRAP (Diesel Exhaust)	Experimental	Between-participants	0 and 4 hours
5	Chronic (~20 years)	TRAP	Natural	Between-participants	—

Note. * Chapter 3: Particulate Matter measured as a proxy for TRAP exposure during commuting. All experiments were cross-sectional

Chapter 2 – Acute Particulate Matter Exposure impacts Approach-avoidance processing after 24 hours but leaves Episodic Memory intact

Abstract

One major component of outdoor air pollution harmful to human health is Particulate Matter (PM). Recent evidence suggests short periods of exposure may result in changes to brain function and therefore behaviour. Immediate effects likely stem from hypoxia, a systemwide lack of oxygen lowering blood-oxygen level in the brain, whereas delayed effects likely stem from inflammatory processes affecting neurotransmission. In this study participants were exposed to either high PM concentrations via burning of a stearin candle, or clean air. During exposure participants completed a Go/No-go task using fearful and happy face expressions to test emotional Approach biases as well as learning and recalling the sequential order and location of 20 object images to test episodic memory. 24 hours following exposure the Go/No-go task and memory recall were administered again. Data from 68 participants (M_{age} = 19.21, SD_{age} = 0.97) indicated that in the Go/No-go task participants in both groups showed the same sensitivity to both emotion expressions on the first testing day. However, the candle exposure group showed a decline in bias to positive-affective stimuli (happy faces) on the second day of testing compared to the clean air condition, indicating a reduction in pro-social behaviour 24 hours following exposure to high concentrations of PM. Inflammation is a good candidate to explain the identified effect as inflammation from non-PM sources causes similar effects after a delay. There was no observable impact of PM exposure on the ability to learn or recall the sequence of objects; this may be due to the use of a training period prior to memory recall.

Introduction

Air pollution (AP) is a global health risk (WHO, 2016). The air we breathe is formed of pollutants from both indoor and outdoor sources, most commonly created through burning. One major component of air pollution is microscopic particulate matter (PM), a mixture of both airborne particles and droplets (Ciencewicki and Jaspers, 2007), formed of multiple components dependent on source (Chow and Watson, 2002). PM is known to be neurotoxic (Harry and Kraft, 2008; Costa et al., 2017), degrading the brain's cellular structures (de Prado-Bert et al., 2018) and a range of literature has identified its involvement in both altered neurodevelopment (Herting et al., 2019) and the onset of neurodegenerative diseases (Peters et al., 2019; Kasdagli et al., 2019; Noorimotlagh et al., 2020). Even the seemingly innocuous act of blowing out candles on a birthday cake can temporarily increase PM concentrations far beyond suggested legal limits and therefore pose a risk to human health.

As described in Chapter 1, for regulatory purposes PM is classified by particle diameter in micrometres (μm). PM_{10} is a measure of the mass concentration ($\mu g\ m^{-3}$) of particles with aerodynamic diameter smaller than 10 μm. $PM_{2.5}$ is a measure of the mass concentration of particles with aerodynamic diameter smaller than 2.5 μm, and PM_1 refers to particles under 1 μm (United States Environmental Protection Agency, 2021a). $PM_{2.5}$ is the often most utilised classification in literature surrounding AP exposure and human health, as particles of this mass can be inhaled into the gas-exchange area of the lungs (Miller et al., 1979) and are small enough to enter the blood stream and translocate to other organs (Du et al., 2016). PM is formed of a variety of chemical components, dependent on source, with examples of PM_{10} being dust, pollen, and mould; and examples of $PM_{2.5}$ being combustion particles (including elemental carbon), organic compounds from unburnt or partially oxidised fuel, oxoacids (particularly sulphuric and nitric acids and their salts), and metals (Oke, 1987, p. 306-307). Blowing out a candle produces primarily elemental carbon and condensed organic compounds, particulate air pollution that mimics particulate traffic-related air pollution (TRAP). TRAP is a ubiquitous source of outdoor air pollution in urban environments where most of the population reside. This simple method of producing AP from a candle allows for experimental manipulation of air quality to investigate effects in a controlled way (Shehab and Pope, 2019) and is the approach used in the current investigation of the cognitive impact of AP.

There are two main mechanisms by which exposure to AP could cause cognitive deficits: hypoxia and neuroinflammation. These are not mutually exclusive but almost certainly operate over different time scales with hypoxia acting quickly and neuroinflammation taking at least several hours to affect cognitive function.

As mentioned above, one potential mechanism of immediate cognitive decline following high AP exposure is hypoxia, a state wherein the brain is starved of oxygen (MacIntyre, 2014). Acute hypoxic events have been shown to induce psychomotor slowing (Noble et al., 1993; Shukitt-Hale et al., 1998), impairment in early visual sensory processes (Tsarouchas et al., 2008), working memory deficits (Asmaro et al., 2013), and changes in executive function (Shukitt-Hale et al., 1998; Asmaro et al., 2013) in healthy human participants. In contrast, Komiyama et al., (2015) identified no significant differences in performance or response times in a Go/No-go or Spatial Delayed Response task following hypoxic compared to normoxic (normal oxygen level i.e., 0.21*760 ~160 millimetres of mercury, mm Hg) conditions, highlighting that evidence is mixed (McMorris, et al., 2017). Overall, acute exposure to hypoxic conditions (partial pressure of oxygen, pO_2, below 60 mm Hg) may impact an array of cognitive functions during or immediately following brief exposures. Interestingly, one study collected the inflammatory biomarker interlukin-1beta (IL-1β), a systemic inflammatory cytokine, and brain-derived neurotrophic factor (BDNF) which plays an integral role in synaptic plasticity (Lu et al., 2008) and suggested that cognitive impairments related to hypoxia may further be explained by changes in systemic circulating levels of these and other biomarkers reflecting neuroinflammation (Li et al., 2012). If PM exposure causes a sufficient reduction in oxygen-content in the blood, one might expect cognitive effects immediately following exposure.

Inflammation itself is a strong candidate to explain cognitive dysfunction following air pollution exposure; it is known that exposure to PM causes a rise in systemic inflammation (van Eeden et al., 2001) and a range of experimental evidence suggests that this can occur between four and twenty hours after air pollution exposure (Behndig et al., 2006; Xu et al., 2013; Nightingale et al., 2000, Salvi et al., 2000). One study identified that high levels of inflammatory biomarkers, notably IL-6 and IL-8, persisted 24 hours after exposure to high ambient concentrations of $PM_{2.5}$ (Zhang et al., 2020). Importantly, this systemic inflammation response is thought to also initiate a neuroinflammatory response through either transport of circulating cytokines across the blood-

brain barrier (Banks and Erickson, 2010) or the activation of microglial cells (Shabab et al., 2017) with the resultant inflammatory processes in the brain altering neurotransmission.

Indeed, mild systemic inflammation induced by vaccination is known to produce subtle cognitive deficits in memory (Harrison et al., 2014; Reichenberg et al., 2001); attention (Balter et al., 2019; Allison and Ditor, 2014), and importantly social-emotional processing (Balter et al., 2018; Moieni et al., 2015) several hours or even a day after injection. There is also a causal link between inflammation, low mood, and social disconnection (Eisenberger et al., 2010) with air pollution linked to both a reduction in prosocial tendencies (Rotton et al., 1978) and an increase in immoral behaviour (Lu et al., 2018). Taken together, this evidence gives rise to the possibility of similar social-emotional and executive function processing problems occurring after exposure to PM. Effects on memory are mixed (Bollen et al., 2017) and some studies show an immediate as well as delayed effect (Reichenberg et al., 2001).

To test the immediate impact of PM exposure on global cognitive functioning, Shehab and Pope (2019) exposed participants to a burning candle (stearin, paraffin, or beeswax) or ambient air (no candle) for one hour before taking part in a global cognitive function task (Mini-Mental State Examination, MMSE), sustained and selective attention task (Ruff 2 and 7), and an executive function task (Stroop task). No significant differences were identified between exposure groups for the attention and executive function tasks, although curiously after candle exposure, global cognitive performance (MMSE) was significantly lower than after ambient air exposure.

This study suggests that after immediate exposure to high concentrations of PM, global cognitive function may be adversely affected, although attentional and executive processes appear to be resistant. Whilst this is a potentially compelling finding, the mechanistic underpinnings of the results are unclear, casting doubt as to whether effects truly stemmed from AP exposure or not. Whilst an immediate reduction in cognitive function is associated with hypoxia, this is generally associated with an overall reduction in global brain processing ability and does not explain why poorer performance in Shebab and Pope's (2019) study was not observed across all tasks. One explanation could be the tasks themselves. Whilst the Ruff 2 & 7 and Stroop task are common psychological tasks investigating short-term changes in cognition and showed no immediate effects of AP exposure, the MMSE is a clinical measure which is not valid for non-clinical use (Gluhm et al, 2013) and has questionable suitability in the context of this study. Despite difficulties in interpreting the findings from this study, the paradigm itself is promising and elegantly simple,

allowing for a low-cost, controlled method of increasing PM concentrations without the need for specialist equipment (See Chapter 4).

As reviewed in Chapter 1, an array of research into chronic associations indicate a well-established link between higher concentrations of common pollutants and poorer working memory, attentional, and executive functioning processes. However, relatively few studies have investigated the acute impact of PM exposure on these functions. Two main cognitive functions were selected to test: episodic memory and social-emotional attention. The former was selected because episodic memory requires the hippocampus, which contains a high density of cytokine receptors (Lechan et al., 1990; Schöbitz et al., 1993) and may be particularly impacted by a neuroinflammation response. Moreover, previous literature indicates disruption of hippocampal-dependent memory functions during acute inflammation (Czerniawski et al., 2015). Social-emotional processing was selected due to the range of previous literature discussed above that points to emotion discrimination deficits following inflammatory challenge and diminished pro-social tendencies following air pollution exposure.

To test the potential of hypoxia or neuroinflammation as a cause of cognitive deficits, the present study utilised a two-day design. Participants were exposed to a smouldering candle for 20 minutes prior to and continuously throughout cognitive testing. The same procedure was used 24 hours later as participants underwent a second day of testing. This allowed the investigation of both immediate and delayed impact of cognitive processing following air pollution exposure.

Social-Emotional Processing

It is known that attentional and emotional response mechanisms are closely related (Fenske et al., 2005) as a complex relationship between visual perception and emotion regulation systems of the brain (Adolphs, 2009) work to maintain goal-directed attention and select appropriate responses to stimuli (Compton et al., 2003). Therefore, to test social-emotional cognition, the current study used an attention-based Go/No-go task with face stimuli. Face expression (happy or fearful) defined the ‘go’ classifier so that on some trials a speeded bar press (approach response) was required to the appearance of a happy face and no-go (avoid) responses to fearful faces. On other trials (separated by block) these responses were switched (approach fearful; avoid happy).

The expectation in this task is that all participants will be more willing to approach a positive affective stimulus (happy face) than a negative affective stimulus (fearful face) due to

underlying emotion regulation processes (Elliot, 2006) and this bias should be evident from more accurate discrimination ability for happy versus fearful targets indicating increased sensitivity. Air pollution exposure could affect such biases by two different means: Firstly, it may alter expression discrimination, resulting in low response accuracy regardless of target expression, i.e., the purely perceptual component of this task. If this were the case, expression sensitivity (measured by d′) would be significantly lower for the pollution exposure group compared to the clean air, regardless of target expression.

The second potential outcome is that approach-avoid biases are altered as a result of air pollution exposure. In normal circumstances, the pre-potent tendency to approach positive stimuli and avoid negative stimuli should produce a bias in accuracy, favouring performance when the target is happy, and resulting in a lower d′ score for fearful targets compared to happy targets. Air pollution could disrupt this pre-potent motivational processing in favour of negative-affective stimuli which would manifest in higher d′ values for fearful than happy stimuli.

Episodic Memory

Due to the complexity of episodic memory processing, a task containing both spatial and temporal (serial) learning measures was used. Whilst both are thought to be hippocampal dependent, different functional networks have been identified in the retrieval of each sub-domain (Ekstrom and Bookheimer, 2007). The task used a 'list learning' training procedure followed by an immediate memory test on the first testing day and a delayed memory test on the second. This allowed for an assessment of immediate deficits to learning capacity, indexed by number of training runs needed to meet a criterion of accuracy, as well as assessment of immediate and delayed memory capacity in both temporal and spatial domains, indexed by accuracy of recall of serial order and spatial location of learned items.

Importantly, if hypoxia is the underlying mechanism for changes in cognition due to AP exposure, then differences in task performance for each air exposure condition should be seen in the first testing session. However, if neuroinflammatory mechanisms are responsible for changes in cognition due to AP exposure, and if the neuroinflammatory response is maintained for 24 hours or more, no condition effects on task performance on the first day of testing should be seen; such effects should only be evident on the second day.

Method

Participants

Sample sizes for this experiment were calculated using G*Power 3.1 (Faul et al., 2007) based on effect sizes obtained in three separate studies.

Firstly, Albert et al., (2011) used a Go/No-go task with positive-affective, negative-affective, and neutral stimuli to identify brain areas active during task; there were no separate groups in this study, but behavioural measures indicated error-rate differences for trials with positive-affective versus negative-affective targets indicating difference in sensitivity dependent on emotion. Through extrapolation of the data, Cohen's d = 0.81 for the comparison between positive- and negative-affective error rates to mimic responses to happy and fearful expressions in the current study. Assuming an air pollution group x emotion expression interaction, a medium-large within-between interaction effect size of f = 0.3 and a power of 0.80 were assumed. The result was a required sample size of at least 24 participants in each group to observe an effect of condition (Candle vs. Clean Air) on sensitivity to positive- vs. negative-affective stimuli, albeit through d′ instead of error rate as a measure.

Petzka et al., (2021) used the Memory Arena task to identify changes in spatiotemporal recall ability, albeit they were interested in the influence of activity between task administrations (a period of sleep or wake) as opposed to influence of air pollution exposure as in the current study. They reported Cohen's d = 1.7 for the comparison between sleep and wake groups on change in object sequence performance on the Memory Arena, i.e., describing a 2-way interaction between test administration time (pre vs. post) and condition (sleep vs. wake). Recalculating to get Cohen's f (0.5d), this relates to a very large interaction f effect of 0.85. Assuming air pollution exposure would have lower influence on change in performance than sleep, a medium-large within-between interaction effect size of f = 0.3 and a power of 0.80 were assumed. Again, the result was a required sample size of at least 24 participants in each group to observe an interaction effect of condition (Candle vs. Clean Air) on changes to sequential (serial) recall performance, with the same assumed to be true for spatial recall.

Finally, sample size was checked against results obtained by Shehab and Pope (2019) who used the Mini-Mental State Examination (MMSE) to identify changes in global cognitive functioning before and after exposure to PM through candle burning (within-participants). Through data extrapolation Cohen's d = 0.47 was identified. Assuming the sensitivity of the

Memory Arena and Emotion Recognition Task to detect cognitive changes is higher than that of the MMSE, an effect size of $d = 0.7$ and a power of 0.80 were assumed. The result was a required sample size of at least 26 participants in each group to observe a difference in cognitive function between the Candle and Clean Air independent groups.

Eighty-five Psychology undergraduate students at the University of Birmingham, Birmingham, UK were recruited through an online database and offered research credits on completion of the tasks. Individuals who reported current neurological, psychiatric, inflammatory, or respiratory disorders (e.g., multiple sclerosis, depression, rheumatoid arthritis, asthma), cold or flu symptoms in the past 14 days, vaccination within the last 14 days, or current smoking were excluded. All data from 17 individuals were excluded from all analyses as they had missing data on either testing day ($N = 10$), their depression score was +2.5SDs from group mean ($N = 3$), their sleep quality was +2.5SDs from group mean ($N = 2$), they self-reported not completing the tasks appropriately ($N = 2$), and they engaged in multiple high air pollution exposure activities between test days ($N = 1$). Table 2.1 shows the characteristics of the remaining participants.

Table 2.1

Demographic Characteristics of Candle Manipulation Experiment Sample

Demographic Characteristic	Clean Air Exposure (Day 1) ($n = 41$)	Candle Exposure (Day 1) ($n = 27$)	*t-value*	*p-value*
Mean Age (Years)	19.22 (*0.91*)	19.19 (*1.08*)	0.142	0.888
Sex (% Female)	97.56%	81.48%		
BMI (kg m^{-2})	22.27 (*3.27*)	21.13 (*2.85*)	1.469	0.146
Depression	5.49 (*5.98*)	4.70 (*5.14*)	0.558	0.579
Anxiety	3.68 (*4.50*)	4.44 (*4.52*)	-0.682	0.498
Stress	8.39 (*6.52*)	9.63 (*6.37*)	-0.774	0.442
Sleep Quality (Last month)	5.12 (*1.86*)	5.44 (*1.78*)	-0.711	0.480
Sleep Quality (Overnight)	2.95 (*1.99*)	2.38 (*1.61*)	1.233	0.222
Urbanicity	4.96 (*1.33*)	4.61 (*1.41*)	1.045	0.300

Note. Number in parenthesis indicates standard deviation. No significant differences between groups for any characteristics, providing confidence that between-group comparisons are valid. Value calculations for mental health characteristics are explained within the materials section

Design

All procedures were approved by the University of Birmingham Science, Technology, Engineering, and Mathematics Ethical Review Committee (reference number ERN_18-0487). All methods were performed in accordance with relevant guidelines and regulations. This study used a mixed experimental design across two days. The within-subjects factor was day of testing, (Day 1, Day 2) and between-subjects factor was air quality [Clean Air (Mean $PM_{2.5}$ concentration = 2.69 μg m^{-3}, s.d. = 1.5), Candle (Mean $PM_{2.5}$ concentration = 41.66 μg m^{-3}, s.d. = 14.99)]. Participants were randomly assigned to an air manipulation condition prior to arrival on the first testing day. Participants were also randomly assigned to an air manipulation condition for the second day of testing. However, following no immediate consequences of PM exposure on cognitive functioning, the conditions were collapsed into 2, focusing on exposure on the first testing day and the impact on performance between testing days; this is the reason for differences in the number of participants between the Clean Air (n = 41) and Candle (n = 27) conditions. $PM_{2.5}$ concentrations on testing Day 2 were included in analysis as a covariate where appropriate.

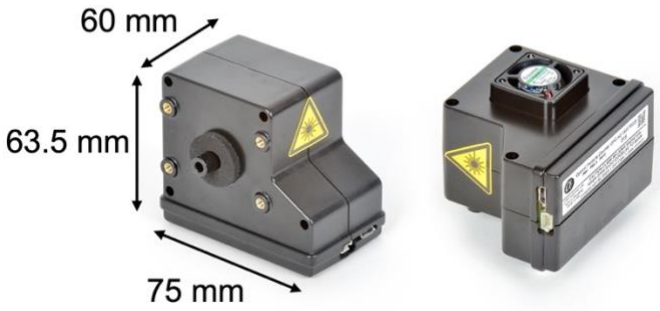
Materials

Software & Equipment

A Windows 8 computer running Matrix Laboratory (MATLAB) version R2018a (9.4; MATLAB, 2018) was used to run the experiment. The Memory Arena and Emotional Discrimination Task were in the form of MATLAB script utilising the Psychophysics Toolbox version 3.0.14 (Brainard, 1997). Alphasense OPC-N2 particulate matter sensor (Figure 2.1) was used to measure concentrations of PM_1, $PM_{2.5}$, and PM_{10} throughout participant exposure; this low-cost sensor has been validated in comparison with standard reference instrumentation (Crilley, et al, 2018) assuming a correction is applied. A Lavender-fragrance plug-in air freshener was used on the lowest setting to mask air smell. 100% stearin candles (height: 19cm, radius: 22mm) made from animal fat (IKEA, 2021), were burned to increase PM concentrations in the candle condition. A digital forehead thermometer (Paryvara, 2016) was used to assess participant temperature during each session as a check to ensure they were unlikely to be suffering from sickness-related inflammation on either study day (i.e., check for study exclusion criteria).

Figure 2.1

Alphasense OPC-N2 Sensor (Alphasense OPC group, 2020)



Note. Left image provides sizing and shows inlet pipe. Right image shows small fan which runs when the instrument is on to control flow of air through inlet

Alphasesnse OPC-N2

This instrument (used under factory settings) measures the light scattered by individual particles carried in an air stream through a laser beam. These measurements are then used to determine the particle size (through determining the intensity of light scattered based on Mie scattering theory) and particle number concentration. Particles are sorted into 16 size bins in the OPC-N2, covering particle sizes from 0.38 to 17 µm. Particle size and concentration is then used to determine particle mass loadings (PM_1, $PM_{2.5}$, or PM_{10}) using default values of sample weighting factors defined by the European Standard EN481. In short, each size bin has a different factor which is multiplied by the total mass of particles in that bin, then certain bins are summed to create values for PM_1, $PM_{2.5}$, and PM_{10}. The instrument calculates assuming a spherical shape, particle density of 1.65 g ml^{-1}, and refractive index of 1.5+i0 (Alphasense, 2015).

This low-cost instrument was chosen in place of OPC reference instruments as they are 30-50 times the cost (Pope et al., 2018), beyond the scope of the grant. Values for PM mass loadings were corrected (Crilley et al., 2018) assuming an efflorescence value of 0.62 for mixed aerosol particles of inorganic and organic compounds of atmospheric relevance (Svenningsson et al., 2006) with the knowledge that during candle extinction (whereby the candle is in smouldering state) this is characterised by a prevalence of organic matter compared to the higher prevalence of elemental carbon during steady burn and sooting (Pagels et al., 2009). Following instrumentation failure of a relative humidity (RH) and temperature sensor, RH was assumed to be 35% within the testing room, a low humidity typical of office buildings (Scott, 2017; Hedge et al., 1994). These

assumptions were made on the basis that inside of the testing room is essentially a microclimate and origins of the circulating air are a combination of ingress of air from ill-fitting windows and mixing of interior air as the door was opened and closed. The room was manually ventilated through opening windows and doors between exposures.

Vernier CO_2-BTA

CO_2 concentrations were measured under a number of conditions using the Vernier CO_2-BTA switched to the 'Low' ranges, covering 0-10,000ppm (Vernier, 2021). This sensor measures CO_2 concentration using infrared radiation (IR) generated using a small lightbulb at one end of a tube and detector at the other. As ambient air diffuses through the holes in the sensor tube, CO_2 molecules in the air absorb IR. The detector measures the IR at the other end of the tube than the light source, and converts the detected IR into ppm, i.e., less IR detected means higher concentrations of CO_2 are present.

Questionnaires

The Pollution Exposure and Lifestyle (PEL) questionnaire was formulated in-house to identify potential participant inflammation levels on the days of testing, previous residential locations for urbanicity measures (a proxy for chronic pollution exposure), and demographics.

The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) was used to measure objective and subjective sleep quality within the last month. Participants answered this 10-item questionnaire and received a score between 0 and 21 with higher numbers indicative of worse sleep quality. A modified version of the PSQI was created to measure sleep quality the night before testing day 2 with a maximum score of 16 indicating poorer sleep quality.

The Depression, Anxiety, and Stress Scale, DASS (Lovibond and Lovibond, 1995) was used to identify recent participant depression, anxiety, and stress. Participants rated to what extent 42 statements applied to them over the past week on a scale of 0 to 4 (Did not apply at all - Applied to me very much, or most of the time). Higher scores indicate higher levels of psychological distress, with a maximum of 42 available for each metric (depression, anxiety, and stress).

Urbanicity Score

Urbanicity, the impact of living in urban areas at a given time (Vlahov and Galea, 2002) was used as a proxy for air pollution exposure throughout the lifetime. There are higher concentrations of common air pollutants in urban compared to rural areas (van Vaeck et al., 1979), although there can be large variations in pollutant concentrations across one city, and population size itself is not necessarily a good predictor of air pollutant concentrations (Bereitschaft and Debbage, 2013). In addition, lifetime urbanicity itself, not related specifically to air pollution concentration, is associated with neural activation changes (Lederbogen et al., 2011). Despite this, this urbanicity measure was used as a proxy of chronic air pollution exposure due to the significant number of participants who had spent large periods of their lifetime residing in countries other than the United Kingdom. The availability of data and differences in temporal and spatial acuity of international datasets make quantifying comparable pollution exposure estimates between international and UK residents difficult. To quantify urbanicity of UK locations participant residential postcodes were entered into https://www.postcodearea.co.uk/ to identify 1 of 6 classifications from UK Census Data from 2011 of UK Government Rural Urban Classifications. (See Table 2.2). For urbanicity score of international countries, Welsh postcodes, and data with only partial postcode information, population at the time of residency was used to classify urbanicity based on the population classifications in Table 2.2, a similar method to that of Mortensen et al., (1999). Individual participant urbanicity scores were formulated as average values across the lifetime proportioned to time spent in each location.

Table 2.2

Urbanicity Classifications and Associated Scores

Urbanicity Score	UK Government Rural Urban Classification	Population
1	Mainly Rural (rural including hub towns >=80%)	< 1,000
2	Largely Rural (rural including hub towns 50-79%)	1,000 – 10,000
3	Urban with Significant Rural (rural including hub towns 26-49%)	10,000 – 50,000
4	Urban with City & Town	50,000 – 100,000
5	Urban with Minor Conurbation	100,001 – 1 million
6	Urban with Major Conurbation	1 million – 10 million
7	Megacity	> 10 million

Cognitive Tasks

Social-emotional processing was tested using the Emotional Discrimination Task. This Go/No-go task utilised face stimuli of varying emotional intensity with either happy or fearful expressions. Spatial and sequential episodic memory was tested using the Memory Arena (Petzka et al., 2021).

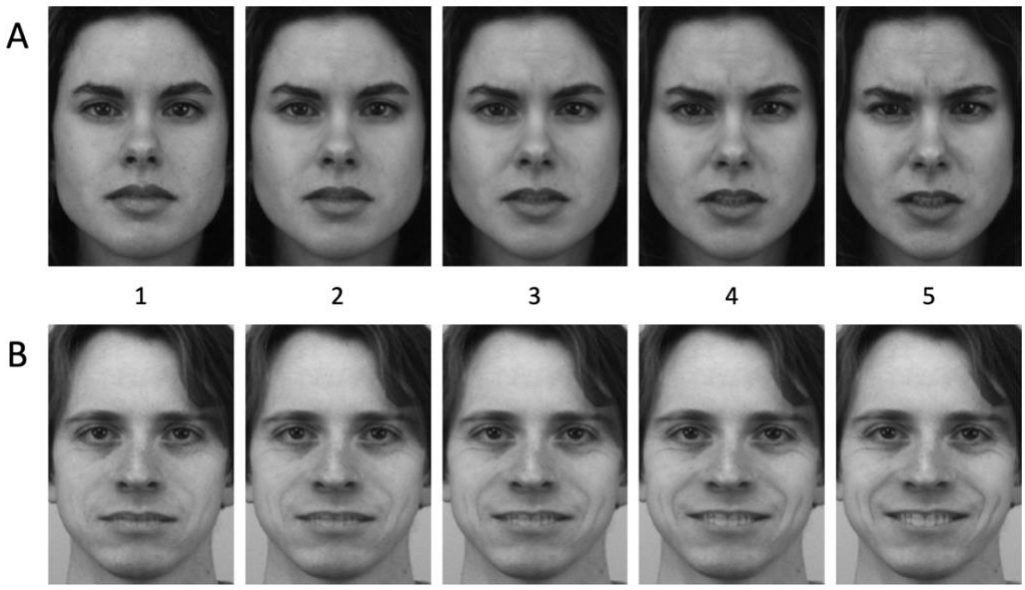
Stimuli

Emotional Discrimination Task. A white centrally presented fixation cross (0.5º in diameter) was used. Iso-expressive faces used in this task were originally created by Gómez-Cuerva (2011) by morphing neutral and expressive faces of the same person in varying proportions. Faces were selected from Karolinska Directed Emotional Faces set (Lundqvist et al., 1998). Gómez-Cuerva measured face expression detection as a function of percent expressive face (versus neutral) in each morph and then interpolated the % value needed for each face to produce a group average probability of correctly detecting an emotional expression on .16 (level 1), .31 (level 2), .50 (level 3), .69 (level 4), and .84 (level 5) of trials. These values correspond to equally space z-values and the resulting morphs have been used to assess sensitivity to face expression unconfounded by individual face features (Gómez-Cuerva and Raymond, 2011). Here, intensities 1 through 4 were used. (See Figure 2.2). Each face image was presented centrally. The background colour was grey, (red-green-blue coordinate, RGB [128, 128, 128]) and explanatory text and fixation crosses appeared in white, RGB [255, 255, 255].

Memory Arena. 20 object images were randomly selected from a total of 50 common inanimate and animate objects from Konkle et al., (2010). These 20 images were presented in full colour, centred inside a white 90x90 pixel square. See Figure 2.4 for an example of these images. A circle divided into four equal segments made up the ‘arena’ which would be populated by the object images. These four segments were four different scenic landscapes: arctic landscape, desert, sea, and autumn forest. (See Figure 2.4A).

Figure 2.2

Example Iso-expressive Face Stimuli used for the Emotional Discrimination Task



Note. **A**: Fearful and **B**: Happy stimuli ranging from **1**: Neutral intensity to **5**: Expressive intensity are shown here. Only expressivity 1 though 4 were utilised

Procedure

Emotional Discrimination Task. See Figure 2.3 for the sequence of displays in each trial. For each block participants were instructed to respond to faces displaying the target expression (happy or fearful) and inhibit response to the other expression (fearful or happy, respectively). Participants responded as quickly as possible by pressing the keyboard spacebar using their dominant hand. Target expression was alternated across successive blocks; the target on the first block was counterbalanced across participants. For each trial, a fixation cross was presented for 400 ms; followed by an expressive face image for 600 ms, or until response. Feedback was given for 600 ms, either 'correct' in green, RGB [0, 255, 0], for hits and correct rejections, or 'incorrect' in red, RGB [255, 0, 0], for misses and false alarms. Six blocks of 48 trials were presented, each containing 32 target (Go) images (two thirds) and 16 non-target (No-go) images (one third). Stimuli had emotional intensities of 1, 2, 3, or 4, split equally between Go and No-go trials in each block. There were therefore four outcomes of each trial (Harvey, 1992): a hit (correct "Go" response to target expression); correct rejection (correct "No-go" inhibitory response to non-target expression); miss (incorrect "No-go" to target expression); and a false alarm (incorrect "Go" response to non-target expression). (See Table 2.3).

The metric d′, a measure of expression sensitivity, was indexed by Z-score Hit Rate [#Hits / (#Hits + #Misses) minus Z-score False Alarm Rate (#False Alarms / (#False Alarms + #Correct Rejections)]. A low score indicates less sensitivity to, i.e., a greater difficulty in distinguishing, a stimulus signal.

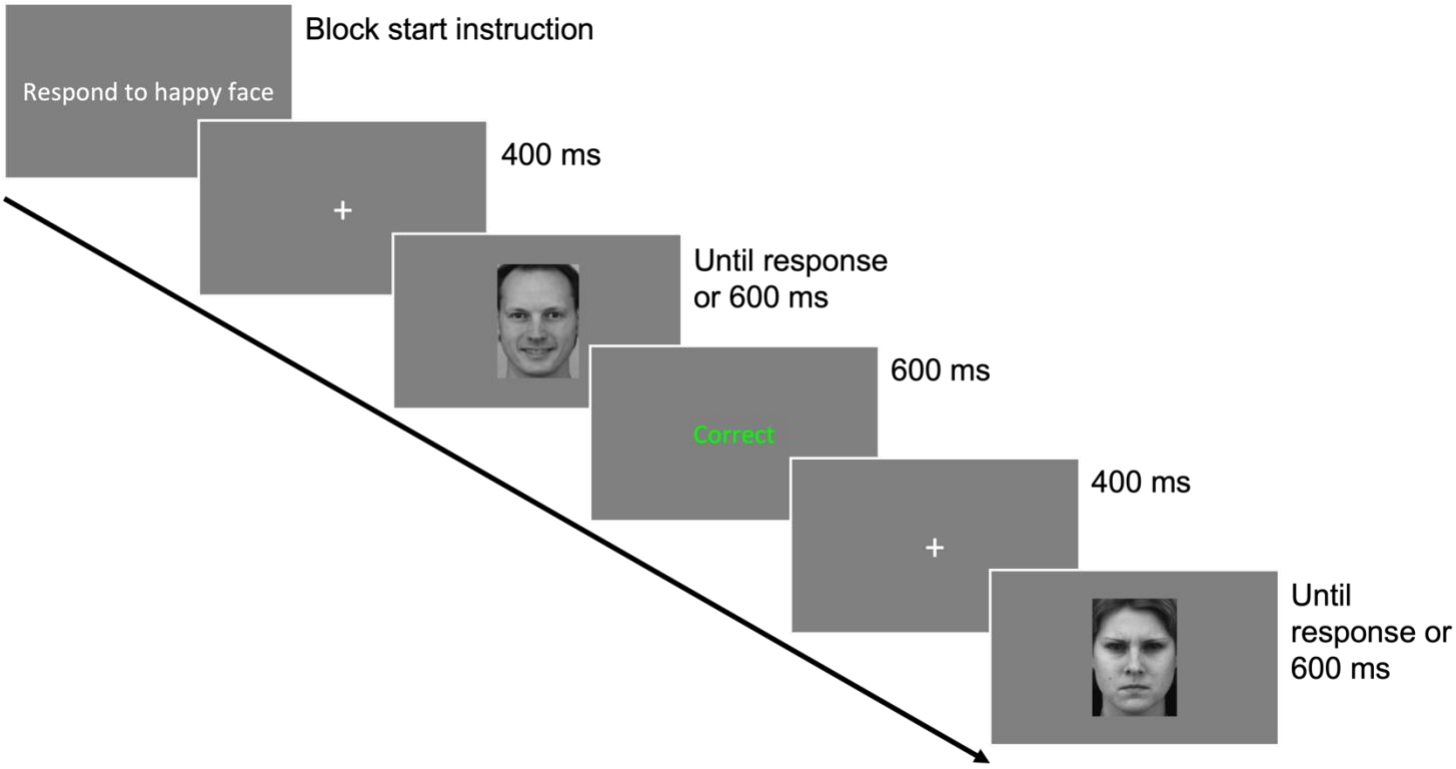
Table 2.3

Contingency Table showing all possible Trial Outcomes

		Stimulus Signal	
		Present	Absent
Participant Action	Response (Go)	Hit	False Alarm
	Inhibition (No-go)	Miss	Correct Rejection

Figure 2.3

Illustration of the Emotional Discrimination Task



Note. Each trial began with a fixation cross presented for 400 milliseconds (ms), followed by the target array for 600 ms or until participants responded. The task was to respond as quickly as possible (spacebar press) if the face matched the instructed expression or inhibit response if the expression differed

Memory Arena

Learning Phase. Participants were first shown the circular 'arena' split into four equal sections. A succession of 20 object images were presented with each appearing in a pseudo-random location within this arena. Objects could appear anywhere within the circle that was not taken up by another image, including on boundaries between the four sections. After each object's appearance participants were required to click on the object after memorising its location. The object image then disappeared, and the next image was presented. This process was repeated for all 20 images, each having a unique location within the arena. Participants were also tasked with remembering the sequential order of the objects as they appeared. There was no time limit for this phase, as the duration each object stayed on the screen depended on participant interaction (clicking).

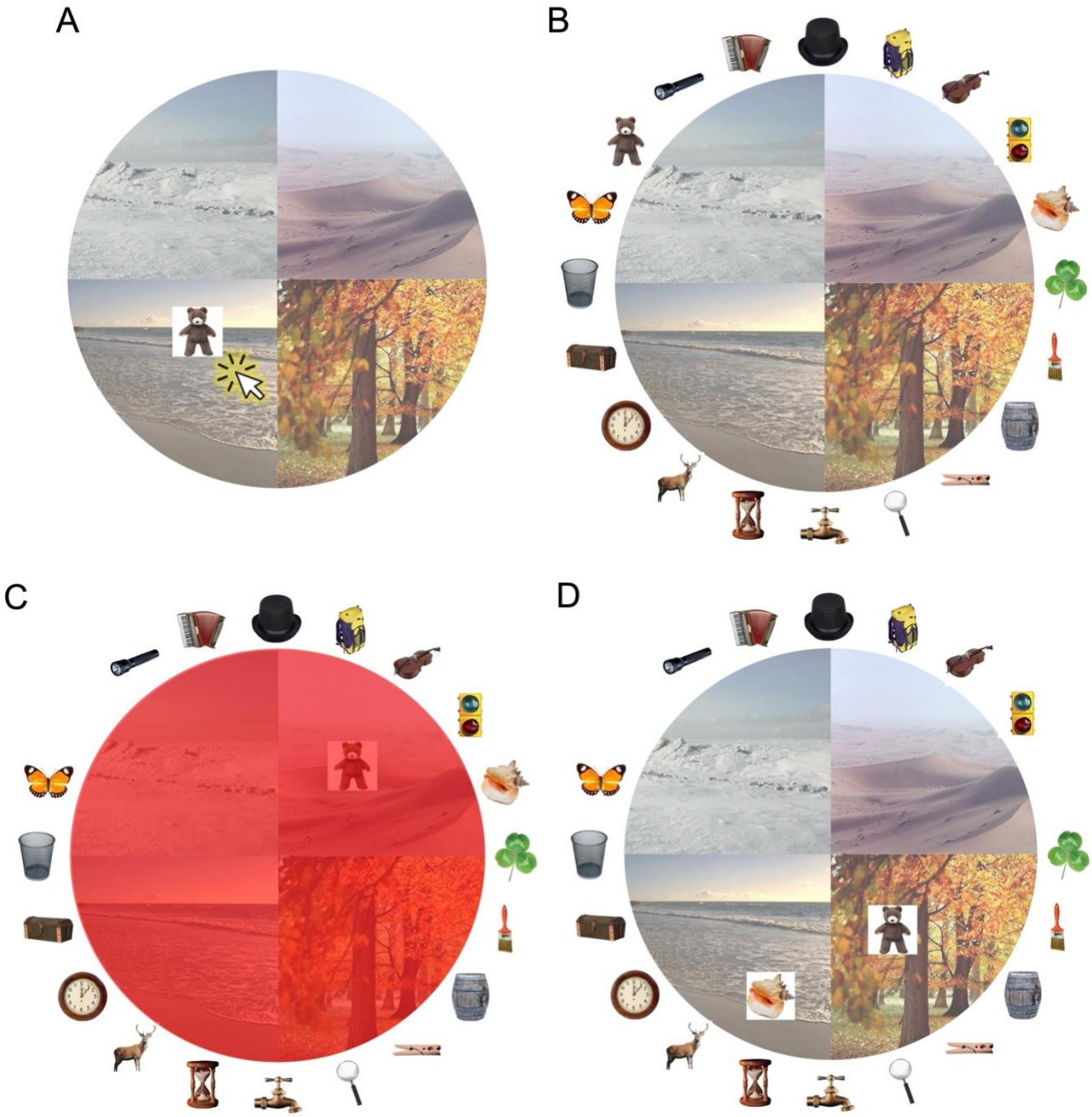
Training Phase. Participants were then presented with all 20 object images in random order outside the edge of the arena. (See Figure 2.4B). They were required to place each object in its correct spatial location and in the correct sequential order as presented during the learning phase. Feedback was provided on each trial as the arena either turned red (see Figure 2.4C) for incorrect placement location (less than 25% overlap between placed object location and correct location for the same object) and/or order, or green for correct placement and order. Following incorrect placement and/or order, the correct object was shown in the correct location and the participant moved to the next trial until all 20 objects were placed. Each 20 trials therefore completed a training 'run'. Training runs were repeated with a novel randomised placement of objects outside the arena edge until participants were correct (both spatially and sequentially) on at least 70% of the 20 objects in *two* consecutive training runs.

Immediate Memory Test. Following a 5-minute break, participants were presented with a random placement of the 20 objects around the arena edge and were required to complete one run to place all 20 objects. This was done without feedback, so if an object was chosen incorrectly, or placed in the incorrect location, it remained in place. (See Figure 2.4D).

Delayed Memory Test. 24 hours after the learning phase, participants repeated the singular run test, again without feedback.

Figure 2.4

Illustration of the Memory Arena



Note. **A**: Learning phase, **B**: Training phase, **C**: Feedback during training, and **D**: Test phase

General Procedure

Testing Day 1

Twenty minutes prior to participant arrival, an air freshener was activated in the testing room (4.15 x 2.95 x 3.40 m = 41.6 m^3) and windows closed. Two candles were also lit at this time (Candle condition only) and blown out one minute prior to participant arrival; the air freshener was left running throughout the experiment (both conditions) to mask any scent from the candle. Participants gave informed consent prior to entering the testing room. Once comfortable, the Alphasense OPC-N2 was switched on to measure PM concentrations throughout the experiment. At this time, participants completed the DASS, PSQI, and PEL questionnaires. After 20 minutes of exposure to either elevated PM concentrations (Candle) or room air (Clean Air), participants completed the Memory Arena. The learning and training phases took between 15 and 45 minutes depending on time taken to reach training criteria. During a 5-minute break in the task, participant body temperature was measured. Next, participants completed the Memory Arena test phase (5 minutes maximum) and then completed the Emotional Discrimination Task, taking approximately 20 minutes.

Testing Day 2

Air quality was manipulated and recorded as described for Testing Day 1. Participants completed the PSQI overnight version, PEL, and had their temperature taken within the first 20 minutes of entering the room. After 20 minutes, participants took part in the Memory Arena delayed test phase (five minutes maximum), followed by the Emotional Discrimination Task (20 minutes) once more. Following completion of the task, participants guessed which air type they had breathed on both testing days, were debriefed, and were provided with course credit.

Data Analyses

Originally the study included candle burning on the second study day. Prior to analysis, it was decided that if no immediate effects were observed in Day 1, the crossover conditions would be collapsed into Day 1 condition only, to investigate the delayed effects of exposure. $PM_{2.5}$ concentration on the second day was included in analysis as a covariate where appropriate. All analyses were conducted at $\alpha = 0.05$ level with Bonferroni corrections for multiple comparisons (Field, 2013, p. 69).

Emotional Discrimination Task

Individual trials were removed if response times were below 200 ms, indicating an anticipation error. As explained above, the metric d′, a measure of expression sensitivity, was indexed by Z-score Hit Rate [#Hits / (#Hits + #Misses) minus Z-score False Alarm Rate (#False Alarms / (#False Alarms + #Correct Rejections)]. This was calculated separately for each target type. A 2x2x2 mixed ANOVA was conducted for d′ with one between group factor pollution group [Clean Air, Candle (on Day 1)] and the within-subjects factors of target expression (happy, fearful) and day of testing (Day 1 or Day 2). A follow-up 2x2 ANOVA was conducted for Δd′ (d′ happy minus d′ fearful) with between group factor pollution group (Clean Air, Candle) and within-subjects factors day of testing (Day 1 or Day 2). Unfortunately, Response Time (RT) data was not analysed due to an error whereby responses longer than 600 ms were not collected for the first 30 participants but were collected for the remaining participants. This mismatch hindered the appropriateness of using the RT measure across all participants and so was left unanalysed.

Memory Arena

Training

The number of training runs needed to reach the learning threshold (70% accuracy on spatial & sequential placement of objects on two consecutive runs) indicated ability to learn the placement and sequence of objects. Time taken to reach the training threshold was also measured. Two independent samples T-tests were used to calculate difference between pollution group for number of training runs and time taken to reach training threshold respectively.

Memory Tests

Spatial placement error was calculated for each chosen object as the straight-line distance in pixels between the centre of the dropped location of the chosen object and the centre of the correct location of that object. Sequential accuracy was scored as correct if the chosen image had been presented just after the previously chosen image regardless of whether the latter had been correctly selected, i.e., if object 6 is chosen after object 5 this is marked as correct even if object 5 was not correct. Spatial error distance and sequential accuracy were each averaged across the 20 trials (one run). Two mixed ANOVAs (between-group factor: pollution group; within-subjects factor: day of testing) were conducted on spatial error and sequential accuracy respectively.

Results

Emotional Discrimination Task

Face Expression Sensitivity – d′

First, an analysis of variance was conducted comparing stimuli intensity (1, 2, 3, 4), emotion expression (happy, fearful), day of testing (Day 1, Day 2), and pollution exposure group (Clean Air, Candle). A main effect of expression was identified [$F(1, 66) = 47.431$, $p < 0.001$, $\eta p^2 = 0.418$, $1\text{-}\beta = 1$] such that d′ was significantly higher for happy (mean d′ = 2.00, s.d. = 0.44) than fearful target stimuli (mean d′ = 1.66, s.d. = 0.59). As expected, this implies that there was a tendency to approach happy faces and avoid fearful faces. There was a main effect of intensity [$F(3, 66) = 174.114$, $p < 0.001$, $\eta p^2 = 0.891$, $1\text{-}\beta = 1$] such that intensity 1 was the least easily distinguished (mean d′ = 0.77, s.d. = 0.30); then intensity 2 (mean d′ = 1.51, s.d. = 0.47); intensity 3 (mean d′ = 2.35, s.d. = 0.71); and intensity 4 (mean d′ = 2.68, s.d. = 0.77); $p < 0.001$ for all pair-wise intercomparisons. (See Figure 2.5). Importantly, there were no significant interactions between air pollution exposure condition and stimuli intensity: [intensity*condition: $F(3, 198) = 1.083$, $p = 0.358$; day*intensity*condition: $F < 1$; day*expression*intensity*condition: $F(3, 198) = 1.573$, $p = 0.197$].

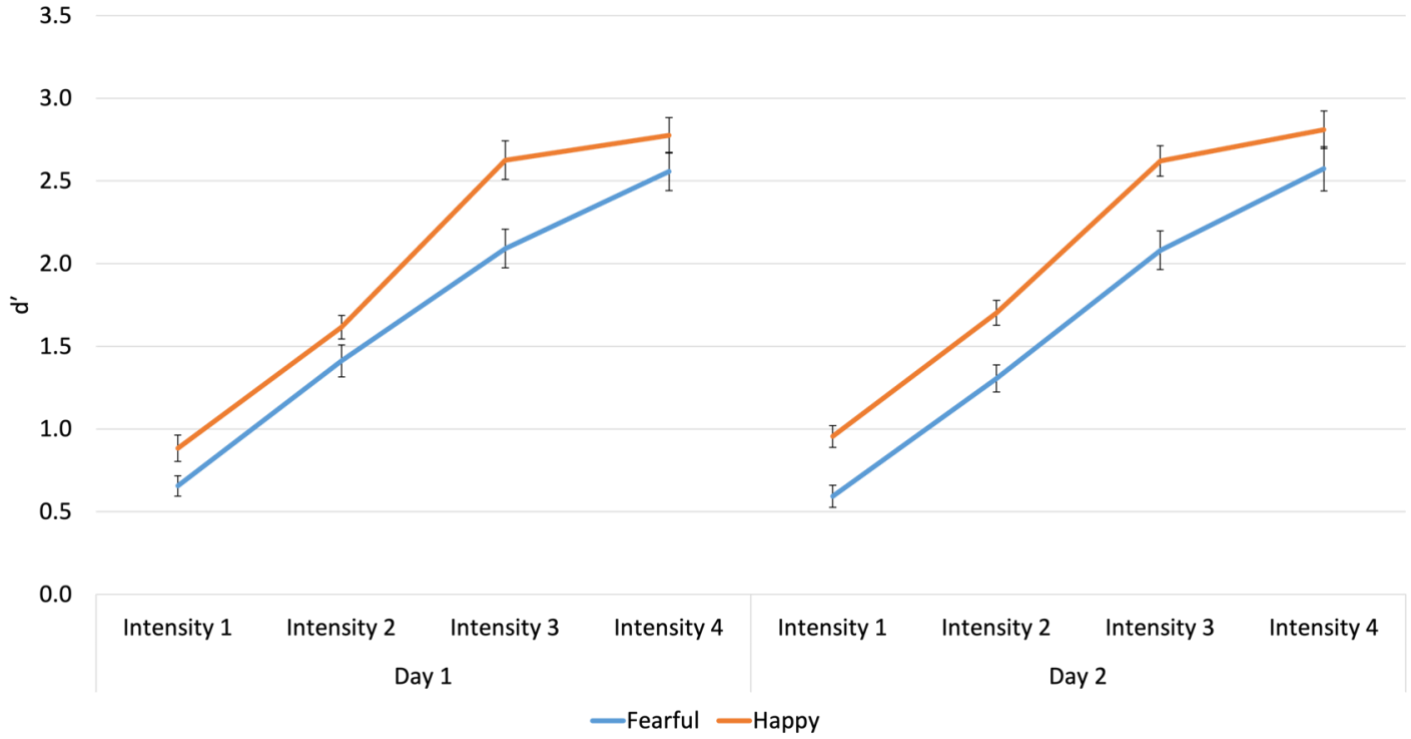
As there were no interactions between emotional intensity and condition, d′ was collapsed into emotion expression, regardless of intensity. The factors included in analysis going forward were therefore expression (happy, fearful), day of testing (Day 1, Day 2), and pollution exposure group (Clean Air, Candle).

It was predicted that d′ should be higher for happy than for fearful face targets reflecting a positive affect Approach bias and that this bias might be negatively affected on Day 2 by pollution exposure on Day 1. Indeed, the 2x2x2 ANOVA of d′ scores showed a significant 3-way interaction of pollution condition, target expression, and day of testing [$F(1, 66) = 5.743$, $p = 0.019$, $\eta p^2 = 0.08$, $1\text{-}\beta = 0.656$]. To explain this interaction and simplify, a Δd′ score was calculated for each participant and Day by subtracting d′ Fearful from d′ Happy. (d′ score for each target expression and Day are shown for each pollution group in Table 2.4). A 2x2 ANOVA (pollution group x day) showed a significant main effect of pollution group on Δd′ [$F(1, 66) = 5.153$, $p = 0.026$, $\eta p^2 = 0.072$, $1\text{-}\beta = 0.609$] and significant interaction between pollution group and day [$F(1, 66) = 5.729$, $p = 0.020$, $\eta p^2 = 0.08$, $1\text{-}\beta = 0.655$] mimicking the 3-way interaction effect described above:

Although Δd′ did not differ between air pollution groups on Day 1 [$t(66) = 0.435$, $p = 0.665$; Clean Air: mean Δd′ = 0.2, s.d. = 0.41; Candle: mean Δd′ = 0.15, s.d. = 0.42], a significant difference in Δd′ was apparent on Day 2, $t(66) = 3.467$, $p < 0.001$, with Δd′ higher in the Clean Air (mean Δd′ = 0.42, s.d. = 0.37) compared to the Candle exposure group (mean Δd′ = 0.1, s.d. = 0.35). (See Figure 2.6A). This indicated an expected difference in expression sensitivity in the clean air group, with happy targets better detected than fearful in comparison to baseline performance. Interestingly, the candle group showed similar performance for both days. Δd′ was compared between pollution group for each testing day which indicated that change on Day 2 in approach-avoidance bias was mediated by pollution group. The Clean Air group showed a greater change (mean change = 0.22, s.d. = 0.46) implying a shift towards a larger positive-affect Approach bias on day 2 compared to day 1; this shift was absent for the Candle group who showed the opposite effect [mean change = -0.05, s.d. = 0.44; $t(66) = 2.395$, $p = 0.019$]. (See Figure 2.6B).

Figure 2.5

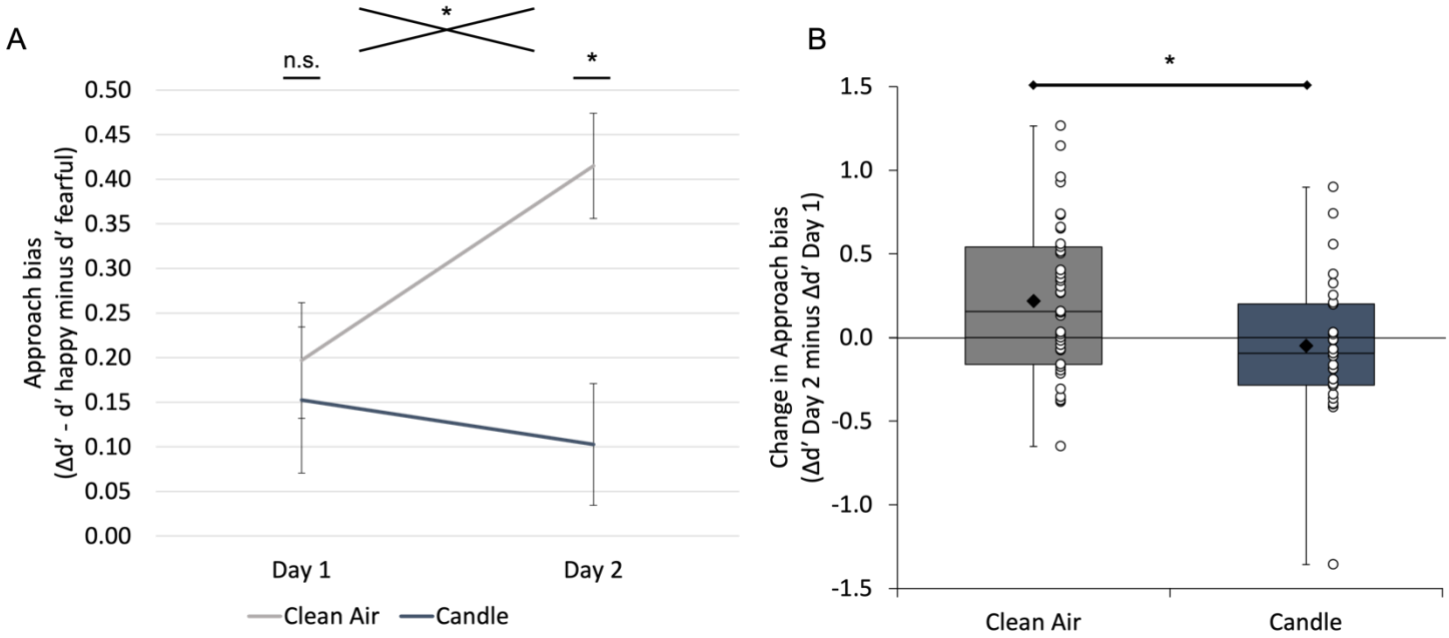
Line Graph showing Sensitivity (d') for each Intensity of Stimuli across both Testing Days



Note. There was a main effect of expression intensity such that participants were more sensitive to intensity 4 expressions than intensity 3, with the same true for all further comparisons. There was also a main effect of expression such that sensitivity to happy faces was significantly higher than fearful

Figure 2.6

A: *Line Graph showing Approach bias [Δd′ (d′ happy minus d′ fearful)] and* **B**: *Boxplot showing Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1) for both Exposure Conditions*



Note. **A**: Significant main effect of pollution group and interaction between pollution group and testing day. Points indicate mean values and error bars indicate standard error. Higher values indicate increased sensitivity to happy compared to fearful target expressions. **B**: The candle exposed group shows a significant change in expression sensitivity in favour of fearful compared to happy stimuli from day 1 to day 2 in comparison to the clean air group. Circles indicate individual participant Change in Approach bias, diamonds indicate group means

As overall expression sensitivity (d′) was not significantly different across day 1 and 2, the differences identified between d′ for different expressions between days are likely mediated by air pollution exposure condition. The different shift in sensitivity across testing days between conditions implies that those in the Candle exposed group increased sensitivity to fearful stimuli on the second day of testing compared to the first, whilst the opposite was true for the Clean Air group. This interesting result suggests that 24 hours after exposure to high levels of particulate matter, participants show a bias towards negative-affective stimuli in comparison to their baseline performance with the opposite shift true for those exposed to Clean Air after the same delay period.

As participants were also exposed to varying levels of PM on the second day of testing, individual average $PM_{2.5}$ concentrations across the second testing day was added into the 2x2x2 analysis as a covariate. The inclusion of second day $PM_{2.5}$ concentrations did not alter any of the

reported results. All other main effects and interactions were non-significant [Pollution group: $F(1, 66) = 1.846$, $p = 0.179$; Day*Expression: $F(1, 66) = 2.267$, $p = 0.137$; all other *F-values* < 1].

To further explore the reason behind these effects, Hit rate and False Alarm rate (which form the d′ measure) were investigated separately to identify if the observed effects were due to higher accuracy in responses or a propensity to incorrectly attend stimuli. No significant 3-way interaction between day, pollution group, and expression was identified for hit rate [$F(1, 66) = 3.838$, $p = 0.054$] or false alarm rate [$F(1,66) = 2.680$, $p = 0.106$] implying that change in either metric individually was not the underlying cause for the changes identified in d′, rather a decrease in expression sensitivity through a combination of both. (See Table 2.4).

Table 2.4

Mean Performance [Hit Rate, False Alarm Rate, d', Approach bias (Δd'), and Change in Approach bias] across Stimuli Expression and Testing Day for both Pollution Exposure Conditions

Metric Description			Clean Air Exposure	Candle Exposure
Hit Rate	Day 1	Happy	80.3% (*7.3%*)	83.2% (*5.3%*)
		Fearful	85.2% (*5.9%*)	87.8% (*4.2%*)
	Day 2	Happy	82.5% (*7.4%*)	84.5% (*4.4%*)
		Fearful	84.7% (*6%*)	89.5% (*3%*)
False Alarm Rate	Day 1	Happy	24.4% (*11.2%*)	22.9% (*7.5%*)
		Fearful	37.3% (*14.8%*)	35.6% (*15.2%*)
	Day 2	Happy	22.5% (*9.5%*)	26.5% (*13.5%*)
		Fearful	39.4% (*15.9%*)	38.1% (*17.6%*)
Expression sensitivity - d′	Day 1	Happy	1.62 (*0.41*)	1.75 (*0.33*)
		Fearful	1.42 (*0.45*)	1.59 (*0.49*)
	Day 2	Happy	1.76 (*0.39*)	1.71 (*0.41*)
		Fearful	1.35 (*0.47*)	1.6 (*0.56*)
Approach bias (Δd′ – d′ happy minus d′ fearful)		Day 1	0.20 (*0.41*)	0.15 (*0.42*)
		Day 2	0.42 (*0.37*)	0.10 (*0.35*)
Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1)			0.22 (*0.46*)	-0.05 (*0.44*)

Note. Standard deviation in parentheses

Memory Arena

The training runs were analysed to identify differences in learning ability between pollution exposure groups. The number of runs taken to learn the sequence was not significantly different between the Clean Air (mean = 7.22 runs, s.d. = 2.23) and Candle (mean = 6.70 runs, s.d. = 2.37) pollution exposure groups [$t(66) = 0.911$, $p = 0.366$]. Similarly, the time taken to complete the training phase was not significantly different between the Clean Air (mean = 20.39 minutes, s.d. = 5.74) and Candle groups [mean = 18.54 minutes, s.d. = 5.55; $t(66) = 1.315$, $p = 0.191$]. This implies no difference in the ability of participants to learn the sequence and location of the 20 objects over all the training runs irrespective of pollution exposure group. Importantly, as the time taken was not significantly different between groups, the average time participants were exposed to the air in each condition did not differ.

Average test run performance for object sequence placement was analysed for each pollution group across the two testing days. A mixed 2x2 ANOVA identified a significant main effect of day such that participants had higher correct sequence placement on the first day test (mean = 86.84%, s.d. = 14.73) compared to the second day test [mean = 71.28%, s.d. = 20.03; $F(1, 66) = 61.391$, $p < 0.001$, $\eta p^2 = 0.482$, $1\text{-}\beta = 1$]. This was expected, as participants were instructed not to actively reconsolidate between sessions. Importantly, no main effect of condition or interaction was identified, *F-values* < 1, implying that exposure to pollution did not affect sequence recall ability or the change in sequence recall ability between test days. (See Figure 2.7A).

Average test run error distance between object placement location and true object location was analysed for both pollution groups across the two testing days. A mixed ANOVA identified a significant main effect of day such that participants had a lower mean error between object placement location and actual object position on day 1 test (mean = 43 pixels, s.d. = 22) compared to day 2 test [mean = 52 pixels, s.d. = 24; $F(1, 66) = 18.408$, $p < 0.001$, $\eta p^2 = 0.218$, $1\text{-}\beta = 0.988$]. In line with the results on sequence recall, no main effect of condition or interaction was identified, *F-values* < 1, implying that exposure to pollution did not affect overall object placement error or a change in object placement error between test days. (See Figure 2.7B).

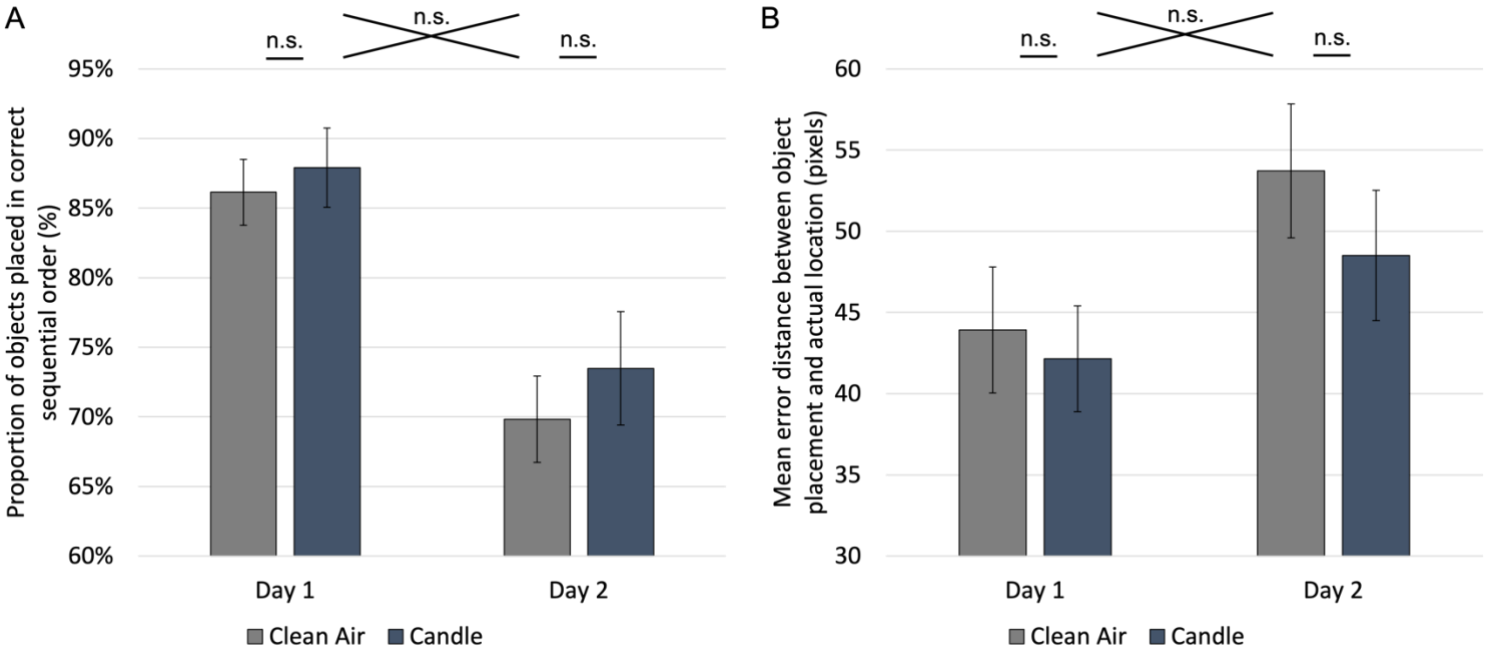
One explanation for these results is a trade-off between learning spatial versus sequential information. However, the training phase required both metrics to be recalled with a 70% success rate for two consecutive runs. To further reject this as a potential factor influencing results, a correlation was conducted between spatial distance error and sequential accuracy on both day 1

[$r(66) = -0.431$, $p < 0.001$] and day 2 [$r(66) = -0.389$, $p = 0.001$]. As both metrics were moderately correlated on both days, it is assumed that a potential trade-off did not influence results of the Memory Arena recall tests.

These results suggest that exposure to high concentrations of particulate matter do not impact episodic memory ability, specifically memory for sequences and object locations. Whilst an interaction was expected between recall ability and pollution group, such that there would be a significant deterioration of performance across testing days for the candle condition, this was not observed. The results suggest that the consolidation and recall of both temporal and spatial information is not impacted by exposure to high concentrations of particulate matter or that this test is not sufficiently sensitive to reveal these effects.

Figure 2.7

Bar Charts showing **A**: *Mean Object Sequence Accuracy and* **B**: *Mean Object Location Error Distance for both Exposure Conditions*



Note. **A**: Significant main effect of testing day identified but no other main effects or interactions. Columns indicate mean proportion correct (%) and error bars indicate standard error. **B**: Significant main effect of testing day identified but no other main effects or interactions. Columns indicate mean error values (pixels) and error bars indicate standard error

Air Quality Measures

Particulate Matter Concentrations

PM_1, $PM_{2.5}$, and PM_{10} concentrations were collected at 1 second intervals when participants were in the room for both conditions across both days. These were then averaged within each session to give average PM concentrations for each participant for each session. Three separate T-tests were conducted to compare average concentrations of PM_1, $PM_{2.5}$, and PM_{10} between the clean air and candle group on the first day of testing. Results of these T-tests were all significant, indicating that average PM_1 concentrations were significantly higher in the Candle exposed group (mean = 28.04 $\mu g\ m^{-3}$, s.d. = 10.6) compared to Clean Air group [mean = 1.57 $\mu g\ m^{-3}$, s.d. = 1.22; $t(66) = -15.891$, $p < 0.001$]; the same for $PM_{2.5}$ concentrations, Candle (mean = 41.66 $\mu g\ m^{-3}$, s.d. = 14.99), Clean Air [mean = 2.69 $\mu g\ m^{-3}$, s.d. = 1.5; $t(66) = -16.587$, $p < 0.001$]; and PM_{10} concentrations, Candle (mean = 53.88 $\mu g\ m^{-3}$, s.d. = 17.46), Clean Air [mean = 11.18 $\mu g\ m^{-3}$, s.d. = 3.04; $t(66) = -15.371$, $p < 0.001$]. (See Figure 2.8).

This shows that blowing out two candles one minute prior to participant testing significantly increased PM concentrations in comparison to the Clean Air condition. All participants in the Clean Air group were exposed to $PM_{2.5}$ and PM_{10} concentrations below WHO 24-hour limits, and $PM_{2.5}$ concentrations below WHO annual limits (WHO, 2005). This was the same for PM_{10} annual concentration limits except for one participant (PM_{10} concentration: 20.85 $\mu g\ m^{-3}$; WHO annual limit: 20 $\mu g\ m^{-3}$). All participants in the Candle condition were exposed for short periods to concentrations above long-time-average legal limits, although it should be noted these limits refer to outdoor air quality.

Carbon Dioxide Concentrations

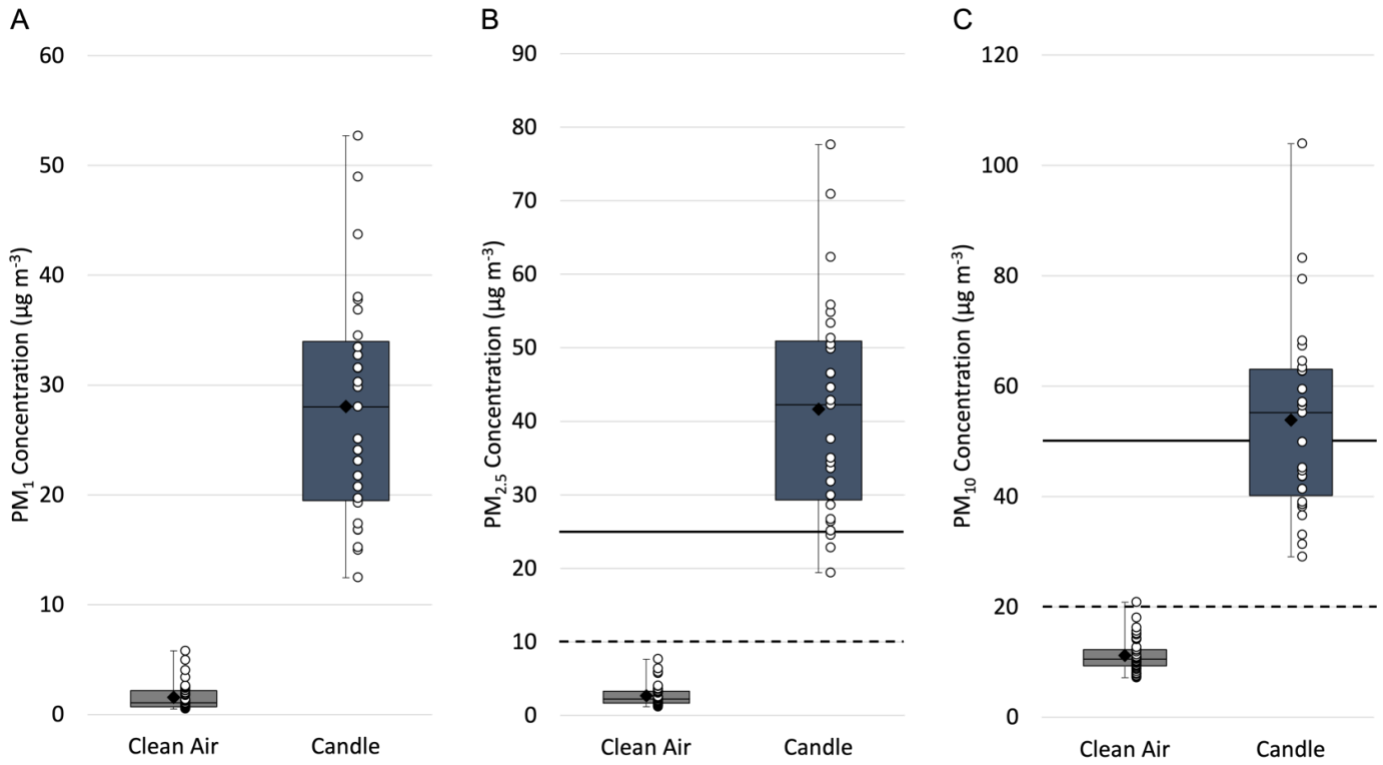
Carbon monoxide concentrations are implicated in hypoxia and neuronal cell death whereas high carbon dioxide concentrations are related to impairment of visual perception (Stepanek et al., 2014) and decline on a range of other cognitive measures (Allen et al., 2016). Carbon dioxide (CO_2) concentrations were recorded subsequently under a number of conditions although carbon monoxide was unable to be measured.

CO_2 was measured under both Clean Air and Candle conditions as described previously, however also under conditions with the testing room occupied (two people: one experimenter and one participant) or unoccupied. Following a review of the data, it was seen that concentrations

increased linearly over time, so initial concentrations (timepoint 0) were compared to later concentrations (timepoint 30) with a mixed 2x2x2 ANOVA [between-subjects factors room capacity (occupied, unoccupied) and pollution exposure (Candle, Clean Air); within-subjects factor time (0 minutes, 30 minutes)].

Figure 2.8

Boxplots showing Mean **A**: *PM_1,* **B**: *$PM_{2.5}$, and* **C**: *PM_{10} Concentrations in the Clean Air and Candle Exposure Conditions*



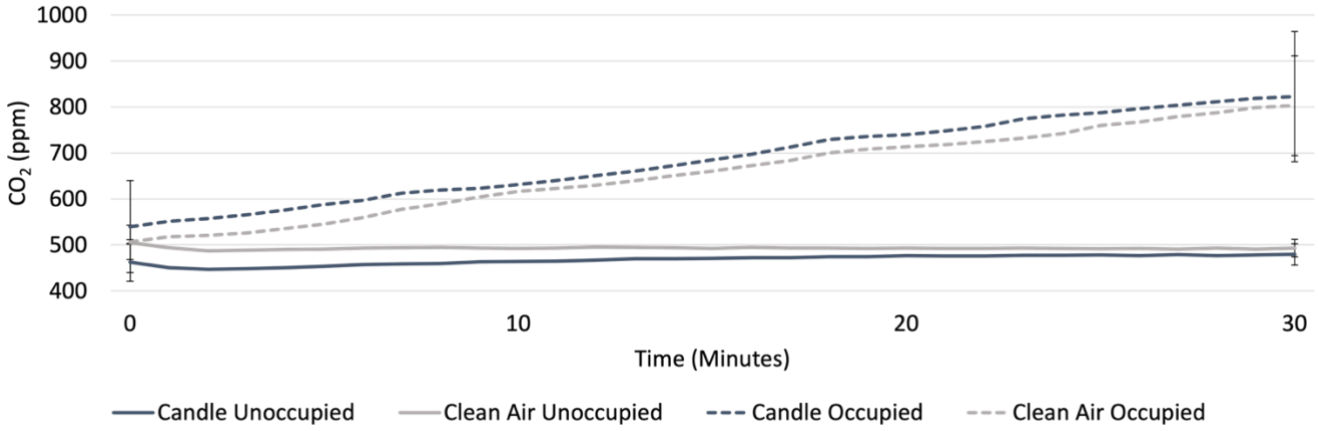
Note. Lower concentrations indicate cleaner air. White circles indicate individual participants, black diamonds indicate group means. Dashed lines indicate World Health Organization average annual concentration limits with solid lines indicating average 24-hour concentration limits.

Importantly, results showed no significant main effect of pollution exposure group or interaction between pollution exposure, time, or room capacity (All *F-values* < 1). This indicated that CO_2 levels within the room were similar for both pollution exposure groups. As expected, there was a significant main effect of capacity [$F(1, 8) = 21.065$, $p = 0.002$, $\eta p^2 = 0.725$, $1\text{-}\beta = 0.979$] such that the occupied room had higher CO_2 concentrations (mean = 668 ppm, s.d. = 175) compared to unoccupied (mean = 485 ppm, s.d. = 32); a significant main effect of time [$F(1, 8) = 67.054$, $p < 0.001$, $\eta p^2 = 0.893$, $1\text{-}\beta = 1$; time 0 (mean = 504 ppm, s.d. = 57); time 30 (mean = 650

ppm, s.d. = 187)]; and a significant time*capacity interaction [$F(1, 8) = 64.756$, $p < 0.001$, $\eta p^2 = 0.890$, $1\text{-}\beta = 1$]. This interaction clearly explains our main effects – concentrations started at similar levels across all groups, and the occupied room (regardless of exposure condition) saw an increase in CO_2 concentrations consistent with respiratory processes of participants and experimenter, whereas the unoccupied condition showed limited change (a consistency of concentrations) between 0 and 30 minutes. (See Figure 2.9). Importantly, this shows that CO_2 concentration did not differ between pollution exposure conditions, so identified cognitive effects are due to PM rather than CO_2 changes.

Figure 2.9

Graph Depicting Change in CO_2 Concentrations (ppm) during Clean Air and Candle Manipulations with Occupied (2 persons) and Unoccupied (0 persons) Conditions



Note. Solid lines indicate CO_2 concentrations in an occupied testing room with dashed lines indicating unoccupied. Dark blue lines indicate candle condition, grey lines indicate clean air

Other Metrics

Participants' condition guesses were compared to their condition. For the first day, there was no significant association identified between reported pollution condition and actual pollution condition [$\chi^2(1, N = 82) = 0.078$, $p = 0.780$], implying participants were blind to their condition. Another χ^2 test indicated that participants were also blind to exposure on day 2 [$\chi^2(1, N = 77) = 0.291$, $p = 0.589$].

Participant scores on the PSQI, DASS, and other demographic details can be found in Table 2.1 above. Importantly, there were no significant differences identified between pollution groups

for any measured characteristics, providing confidence that between-group comparisons are valid and that the identified results were not due to individual differences.

Body temperature was measured once per session to assess possible sickness unrelated to the air pollution exposure; it would not be expected that exposure to AP causes body temperature changes. As no body temperature was higher than 36.7℃, it can be assumed that participant illness was also not an underlying cause for the results reported in this Chapter. However, self-reported feelings of sickness were not explicitly collected.

Discussion

In this study, participants were exposed to either high concentrations of particulate matter or clean air. After exposure participants completed an episodic memory task and Go/No-go task with a social cognition component. After 24 hours these were tested once more. Air pollution exposure caused a shift of expression sensitivity whereby a second day of testing enhanced positive affect Approach biases in those exposed to clean air on Day 1, with this effect statistically absent for those exposed to polluted air on Day 1. AP exposure on Day 1 did not impact participant ability to learn or recall the sequential order and spatial location of 20 objects; performance was the same as those exposed to clean air on Day 1.

This is the first time acute particulate matter exposure has been studied with relation to social-emotional processing. As overall d′ was not significantly different between air exposure groups, the ability to discriminate between facial expressions, a purely perceptual aspect of face processing, is left intact following air pollution exposure. As there were no identifiable group differences in Approach biases on the first testing day, the AP-mediated shift in sensitivity bias towards negative-affective stimuli on the second task administration is likely due to an inflammation response. The affective Approach biases remained significant when controlling for $PM_{2.5}$ exposure on the second testing day.

The anatomically and functionally connected brain areas involved in emotion regulation are complex (Adolphs, 2009) with a relationship between frontal and cortical areas critical for social cognition. There is evidence that these brain areas may be sensitive to negative effects of air pollution exposure (Calderón-Garcidueñas et al., 2002; Calderón-Garcidueñas et al., 2003), providing a reasonable assumption that the changes in social cognition identified are indeed resultant from AP exposure. Evidence also suggests an association between increased pro-inflammatory cytokines and an increase in negative attentional bias (Boyle et al., 2017; Cooper et al., 2018; and Gray et al., 2018). Although these studies are in patient populations, this provides further indication that inflammation is the cause of the identified change in Approach bias in the current study.

Whilst the mechanistic underpinnings of the identified effects cannot be confirmed, there are two plausible psychological explanations: Firstly, effects may be due to task practice. Approach bias was similar for all participants on the first testing day, the first time they completed the task, whereas the identified changes were on the second day, 24 hours later. The short time

between the administering of the task mean that participants will be familiar with what is involved in the task during readministration. This could lead to a lack of frontal control needed to successfully complete the task on the second day of testing, therefore task responses may reflect a more relaxed or unconscious processing. The implication here is that the results of Day 2 (in comparison to Day 1) may show the underlying bias in processing of sensory information after AP exposure due to a lack of frontal control following task practice.

A second explanation is that effects could be due to changes in top-down control processes (Mohanty and Sussman, 2013). Performance is the same on the first testing day and by the second day, those exposed to air pollution are undergoing brain process changes related to inflammation-related "sickness behaviour", known to result in social withdrawal (Eisenberger et al., 2010). In this version of events, those exposed to AP show less sensitivity to positive-affective stimuli, i.e., a smiling face, compared to their clean air counterparts.

It is not possible to substantiate either attentional mechanism using the current data. Consequently, brain activation measures such as Electroencephalography (EEG) or functional Magnetic Resonance Imaging (fMRI) may be useful to elucidate changes in brain function during task administration to provide evidence for the mechanistic underpinnings.

With "sickness behaviour" being a reasonable explanation, it is important to note that self-awareness of sickness-related symptoms could itself influence behaviour (Keogh et al., 2013), potentially confounding the results. As participants were not explicitly aware of their condition and body temperature measures were always within a healthy range on both testing days, this possible explanation can be dismissed. However, even changes in mood can impact perception. For example, melancholic individuals show differences in both bias and discriminability to verbal emotional stimuli compared to a control group (Hyett et al., 2014). In their study, Rotton et al., (1978) highlighted that the air pollution-mediated reduction in pro-social tendencies identified were related to mood and social isolation, although notably the pollutant-exposed room was odorous which was controlled for in the present paradigm. Although low mood symptoms are both a response to and mediator of inflammation, and thus sickness behaviour (Eisenberger et al., 2017), in future participant mood and sickness-related symptoms should be collected to rule out affect, arousal, and self-report sickness symptoms as possible mediators of Approach bias.

This study showed no changes in learning or ability to recall the order and location of 20 object items. These results are somewhat surprising given the hippocampus, the brain area critical

for the storage and retrieval of memory traces (Tulving and Markowitsch, 1998), is thought to be particularly impacted by neuroinflammation following AP exposure (Costa et al., 2017). Although, the relationship between the hippocampus and inflammation is complex with some evidence suggesting that inflammatory agents may modulate neuronal response to improve, rather than disrupt, memory (DiSabato et al., 2016).

As is common with episodic memory tasks, recall ability on the Memory Arena relies on sleep-dependent consolidation (Petzka et al., 2021), so it was important that this was accounted for with a sleep questionnaire showing no difference between sleep quality of the two exposure groups. This indicates that exposure to AP did not disrupt the consolidation or recall of spatial location or temporal order of the objects. One explanation for the findings may be the learning and training phases of the task taking part on Day 1 only, not allowing time for inflammatory processes to take effect. The training phase may have also unintentionally impacted day 2 performance as all participants had training to the baseline level.

One important aspect of the Memory Arena was that it was difficult to perform. It is known that memory traces for object position decay faster than memory for objects themselves (Talamini and Gorree, 2012), and one can be confident that participants did not prioritise learning one aspect of the arena over another based on the correlation between spatial and temporal performance. These strengths suggest a level of validity to investigate the likely very sensitive effects of AP on episodic memory storage and / or retrieval. On the other hand, factors known to influence memory trace strength such as object animacy (Nairne et al., 2017) and affective valence (LaBar and Cabeza, 2006), were not controlled for, possibly playing a strong role in task performance hence eliminating any effects of AP exposure.

The use of a candle to induce high concentrations of PM was a strength of this study, as this was low-cost and repeatable measure significantly increased concentrations of PM_1, $PM_{2.5}$, and PM_{10} in the Candle exposure group compared to the Clean Air group. However, PM concentrations were measured with a relatively novel instrument (Alphasense OPC-N2) which required the use of a correction algorithm to ensure comparability with standard instrumentation (Crilley et al., 2018). A more recent study suggests that correction algorithm applied to the PM data in this study could be improved (Di Antonio et al., 2018), however this indicates that the PM concentrations may be overestimated rather than underestimated in the current study, highlighting that exposure to lower than reported concentrations may still produce the identified effects.

Whilst candle burning is commonplace indoors, this does not fully represent the complexities of residential (Patel et al., 2020) or outdoor air pollution, which is made up of a variety of components. The contents of PM itself varies dependent on source i.e., higher metal content is often found in PM from outdoor sources such as brake dust from cars (Thorpe and Harrison, 2008). The air fresheners, used to successfully mask the condition for participants, may also have altered the pollutant mix in the room as they are known to produce volatile organic compounds (VOCs). Importantly, VOCs are also a stressor to human health and some may be neurotoxic themselves (Goodman et al., 2020). However, all participants were exposed to the air freshener, so the significance of this factor would have to be dependent on any chemical reactivity between VOCs and PM. The identified social cognitive effects may therefore not be found when removing the influence of VOCs or when other pollutants, involuntarily experienced by urban populations on a day-to-day basis, are considered. The following chapter aims to address this issue by utilising real-world pollution as a quasi-experimental independent variable with the same cognitive measures and similar 2-day design.

Particulate air pollution is known to impact social behaviours in the real world. There is an association between high concentrations of $PM_{2.5}$ and incidence of violent crime (Burkhardt et al., 2019). This study highlights that a change in affective sensitivity bias could reasonably explain a decline in pro-social behaviours such as these. The identified changes in sensitivity towards negative-affective stimuli could alter threat detection, which would be detrimental to adaptive human response behaviour. Similarly, the previously discussed association between social cognition dysfunction (i.e., social withdrawal) and depressive symptoms may suggest AP is a causal factor in the decline of mental health.

Chapter 3 – Acute Exposure to Natural-experimental Particulate Matter impacts Approach-avoidance processing after 24 hours and Immediate Episodic Encoding

Abstract

Previous research utilises fixed site monitors (FSM) to estimate acute natural pollution exposure at the expense of spatial and temporal variability, which can be significant, especially during high-exposure activities such as commuting. In this study, acute natural-experimental pollution exposure was measured with a portable PM sensor during participant commuting whilst in personal vehicles. Learning from prior work on indoor exposure (See Chapter 2), a median split of average PM_{10} concentrations during Day 1 commute was used to split participants into two separate groups (High or Low poollution). Immediately following participant commutes, cognitive tasks were administered (Emotional Recognition Task and Memory Arena); 24 hours later the tasks were administered again. Data from 46 participants (M_{age} = 30.43, SD_{age} = 8.04) indicated that in the Emotional Recognition task participants in the High pollution group showed a decline in bias towards positive-affective stimuli (happy faces) on the second day of testing compared to the Low pollution group, replicating the pattern of results found in the prior work. A regression analysis with data from both studies (N = 114) confirmed a significant negative relationship between Day 1 PM_{10} concentration and Approach bias after 24 hours (on the second testing day) only, although the variance explained by this relationship was small (R^2 = 0.038). The high exposure group took significantly more training runs and time to learn the sequence and location of the 20 objects in the Memory Arena compared to the Low pollution group, indicating difficulties in encoding new information following high traffic-related air pollution (TRAP) exposure. There were no significant differences on recall and no significant relationship between pooled PM_{10} concentration on the ability to learn or recall the sequence of objects. These results provide further evidence that inflammatory mechanisms are a likely cause of a reduction in pro-social behaviour following pollution exposure. Hypoxia may explain the immediate impact on encoding ability following exposure to TRAP, however participant encoding in this relatively small sample strategy may have had a confounding effect on the results.

Introduction

Urban air pollution (AP) is composed of gaseous and particulate matter (PM). The chemical composition of PM differs dependent on source, with PM from outdoor emissions sources containing higher metal content (Thorpe and Harrison, 2008). Outdoor (ambient) air also contains higher concentrations of oxyacids and their salts compared to indoor (Li and Harrison, 1990; Brauer et al., 1991). Importantly, the toxicity of PM depends on chemical differences (Kelly and Fussell, 2012), and it is reasonable to expect the effects of PM exposure on behaviour also to depend on source and location.

One of the major contributors of outdoor air pollution is traffic-related Air Pollution (TRAP), the most ubiquitous source of AP in urban areas. Urban residents experience acute high exposure episodes during morning and evening commutes when roads are busy. The most common components of TRAP are Carbon Monoxide (CO), Nitrogen Oxides (NO_X), Sulphur Oxides (SO_X), Volatile Organic Compounds (VOCs), and PM. Recent evidence highlights pollutant-specific changes in circulating toxicity biomarkers after walking in a high TRAP area (Oxford Street, London) compared to low TRAP area (Hyde Park, London). Importantly, the biomarkers themselves relate to organ-specific toxicity, indicating that certain air pollutants may have different effects on the brain than others (Krauskopf et al., 2018), highlighting the merit in expanding the investigation from proxies (e.g., candle burning) into real-world exposures.

It is common for research connecting AP exposure and human health to use Fixed Site Monitors (FSM) coupled with meteorological data to provide exposure estimates (e.g., Bell et al., 2008). Whilst this may be appropriate for epidemiological research where this methodology provides an indication of high and low pollutant concentrations across over time, when looking at acute effects it should be considered that concentrations of pollutants can vary significantly within small regions (Dai et al., 2021; Pearce et al., 2021; Zhong et al., 2020) producing ‘hot spots’ of high concentrations which can vary rapidly, especially indoors or in vehicles (Che et al., 2019). One mode of transport linked to high levels of pollution exposure is driving, for example, one study highlighted that $PM_{2.5}$ levels were twice as high inside cars than on the adjacent pavement in Atlanta, Georgia (Vreeland et al., 2017), and a study in Guildford, UK, highlighted that whilst drivers spent only 2% of driving time in pollution ‘hot spots’, this accounted for 25% of the air pollutants encountered across total drive time. A reason for this is likely to be high traffic levels; pollution inside cars that are stuck in heavy traffic is as much as 40% higher than when traffic is

moving (Kumar and Goel, 2016). This indicates that during a commute, pollutant concentrations can vary quickly and are heavily dependent on individual factors such as traffic level; it is reasonable to assume that FSMs would not provide information on the spatial and temporal variability needed for studies into acute air pollution exposure considering the dynamics of human movement along with the stirring and mixing of AP induced by weather and differences in urban form.

The present study utilised low-cost PM sensors compatible with portable hardware to collect exposure measurements during commuting in personal vehicles. Whilst factors such as openness of windows and use of air conditioning also play a role in in-vehicle exposure (Chaney et al., 2017), by using personal monitors, these factors can be accounted for, giving a value of pollution concentrations within the vehicle for each participant regardless of differences in vehicular conditions.

The aim of this Chapter is to address the issue of ecological validity and environmental representativeness from Chapter 2 by expanding investigation to real-world exposures during commuting. This study used the same cognitive tasks to assess social-emotional cognition and episodic memory following participant commutes. Average PM_{10} concentrations during participant commutes were measured on the first testing day as the naturally occurring independent variable. To allow for comparison between the studies, two groups were created based on a median split of average day 1 commute PM concentrations. As in Chapter 2, participants returned for a second day to assess the potential for a delayed effect of commuter exposure on cognitive function.

Whilst average PM concentrations are expected to be lower than that of the experimental manipulation in Chapter 2, which may potentially produce reduced effects, the chemical components of PM from outdoor sources may heighten or change previously identified effects. Assuming that participants are exposed to a range of pollutant-species from TRAP during commuting, it is expected that the previously identified Approach bias effect will translate to this natural-experiment exposure paradigm despite lower PM levels.

Method

Participants

Sixty-four staff and postgraduate students at the University of Birmingham, Birmingham, UK were recruited through an online research portal and on-campus advertisements and offered £50 on completion of the tasks. Importantly, these individuals were commuters who travelled to the University by car (either driver or passenger in a personal vehicle). Individuals who reported current neurological, psychiatric, inflammatory, or respiratory disorders (e.g., multiple sclerosis, depression, rheumatoid arthritis, asthma), cold or flu symptoms in the past 14 days, vaccination within the last 14 days, or current smoking were excluded. All data from 18 individuals were excluded from all analyses as they had missing data on either testing day (N = 16), their sleep quality was +2.5SDs from the overall mean (N = 1), and they engaged in multiple high air pollution exposure activities between test days (N = 1). Table 3.1 shows the characteristics of the remaining participants.

Design

All procedures were approved by the University of Birmingham Science, Technology, Engineering, and Mathematics Ethical Review Committee (reference number ERN_18-0487). All methods were performed in accordance with relevant guidelines and regulations. This study used a quasi-experimental design across two days. The within-subjects factor was day of testing (Day 1, Day 2), and between-subjects factor was air quality during Day 1 commute (Low PM_{10}, High PM_{10}). The two air pollution exposure groups were formed using a median split of average PM_{10} concentrations during commute on the first testing day to mimic comparisons made with experimental exposures in Chapter 2. PM_{10} was chosen as the concentration as this measure showed the largest variability (3.94 - 106.27 μg m^{-3}) compared to $PM_{2.5}$ (53.98 - 1.64 μg m^{-3}) and PM_1 (47.88 - 1.14 μg m^{-3}). The median PM_{10} concentration was 22.08 μg m^{-3} [interquartile range (13.49 – 33.55 μg m^{-3})]. All participants above the median value were designated as being in the 'high' pollution concentration group (n = 23) and all below were in the 'low' exposure group (n = 23). See Table 3.1 for overall demographics and demographics of these two independent groups.

Table 3.1

Demographic Characteristics of the Natural-experimental Exposure Sample

Demographic Characteristic	All participants (*n* = 46)	Low PM_{10} (Day 1) (*n* = 23)	High PM_{10} (Day 1) (*n* = 23)	*t-value*	*p value*
Mean Age (Years)	30.43 (*8.04*)	29.13 (*8.76*)	31.74 (*7.21*)	-1.103	0.276
Sex (% Female)	71.74%	56.52%	86.96%		
BMI (kg m^{-2})	26.49 (*5.92*)	24.66 (*3.76*)	28.32 (*7.11*)	-2.182	0.034*
Depression	2.28 (*3.28*)	1.96 (*2.60*)	2.61 (*3.87*)	-0.671	0.506
Anxiety	2.50 (*3.50*)	2.22 (*2.33*)	2.78 (*4.09*)	-0.576	0.568
Stress	6.54 (*5.84*)	5.43 (*4.97*)	7.65 (*6.52*)	-1.297	0.201
Sleep Quality (Last month)	4.28 (*2.15*)	3.96 (*2.18*)	4.61 (*2.10*)	-1.031	0.308
Sleep Quality (Overnight)	2.20 (*1.47*)	2.39 (*1.56*)	2.00 (*1.38*)	0.890	0.378
Urbanicity	5.31 (*1.05*)	5.55 (*0.83*)	5.06 (*1.20*)	1.602	0.116
Day 1 Commute Time (minutes)	26.85 (*13.35*)	28.48 (*14.42*)	25.22 (*12.29*)	0.825	0.414
Day 1 Mean PM_{10} Concentrations	27.41 (*20.96*)	13.83 (*5.30*)	40.99 (*22.03*)		

Note. Standard deviation in parentheses. Low and High PM_{10} columns represent the same datapoints of the 46 participants in the 'All participants' column. T-tests conducted between the Low and High PM groups showed significantly higher average BMI in the High PM_{10} condition compared to Low PM_{10} condition at $\alpha = 0.05$ level. All other comparisons not significant
* indicates $p < 0.05$

Materials

All materials used were the same as in Chapter 2, with some notable differences. Firstly, air quality was not manipulated in the testing room, so candles and air fresheners were not used in this study. Secondly, to record PM exposure during commute (as a proxy for all pollutants), the Alphasense OPC-N2, previously described, was attached to a Raspberry Pi 3 Model B+ (https://www.raspberrypi.org/products/raspberry-pi-3-model-b-plus/) with a power cable for car outlets. (See Figure 3.1). A python code adapted from Crilley et al., (2018) was used to start data collection from the Alphasense OPC-N2 on start-up of the Raspberry Pi, such that participants

plugged the device in during the start of their drive and the device would automatically start collecting air quality data until the car was turned off at their destination.

Figure 3.1

Images Demonstrating the OPC-N2 and Raspberry Pi Setup

General Procedure

Screening Day

Participants were given study information to read and completed the consent form. They then completed the Depression, Anxiety, and Stress Scale (DASS), Pittsburgh Sleep Quality Index (PSQI); and Pollution Exposure and Lifestyle (PEL) questionnaires before being given the pollution sensor for their commute on the testing days.

Testing Day 1

Participants plugged the pollution monitor into their car and placed the sensor on the passenger seat or held by the passenger with inlet facing the driver. The monitor started collecting data automatically once the car engine was switched on, with air sampling every one second until the engine was switched off at the destination (University of Birmingham, Edgbaston campus, B15 2TT, UK). Participants arrived at the testing building immediately following their commute. Once comfortable in the testing room, participants completed the Memory Arena with the same parameters as in Chapter 2. The learning and training phases took between 15 and 45 minutes depending on time taken to reach training criteria. During a 5-minute break in the task, participant body temperature was measured. Next, participants completed the Memory Arena test phase (5 minutes maximum) and then completed the Emotional Discrimination Task, taking 20 minutes.

Testing Day 2

Air quality was recorded on the commute as described for Testing Day 1. Participants then completed the PSQI overnight version, PEL, and had their temperature taken. participants then took part in the Memory Arena delayed test phase (5 minutes maximum), followed by the Emotional Discrimination Task (20 minutes) once more. Following completion of the tasks, participants were debriefed and compensated £50.

Data Analyses

Participants were split into two conditions based on average PM_{10} concentrations on Day 1 commute. PM_{10} concentration on the second day was entered as a covariate where appropriate.

Emotional Discrimination Task

Individual trials were removed if response times were below 200 ms, indicating an anticipation error. As in Chapter 2, d′ (a measure of expression sensitivity) was calculated as the Z-score Hit Rate [#Hits / (#Hits + #Misses)] minus Z-score False Alarm Rate [#False Alarms / (#False Alarms + #Correct Rejections)]. This was calculated separately for each target type and each intensity, a low score indicating less sensitivity to, i.e., a greater difficulty in distinguishing, this expression. As in the previous chapter, RT was not analysed due to data collection error.

Firstly, to identify if stimuli intensity interacted with emotional expression or day of testing a 4x2x2x2 mixed ANOVA with between-subjects factor air exposure group (Low PM, High PM), and within-subjects factors day of testing (Day 1, Day 2), expression (happy, fearful), and emotional intensity (1, 2, 3, 4) was conducted. Following the results of the ANOVA, d′ was collapsed across intensity. Subsequently, a 2x2x2 mixed ANOVA was conducted for d′ with one between-group factor (Pollution: Low PM, High PM) and the within-subjects factors of target expression (happy, fearful) and day of testing (Day 1 or Day 2). Finally, a 2x2 mixed ANOVA was conducted for Δd′ (d′ happy minus d′ fearful) with one between group factor, pollution group (Low PM, High PM) and the within-subjects factor, day of testing (Day 1 or Day 2).

Having confirmed similar findings to those in Chapter 2, the present data was pooled with that of Chapter 2 for simple regression analyses investigating the predictive ability of Day 1 PM_{10} concentration on Approach bias (Δd′) on Day 1, Day 2, and change in Approach bias (Δd′ Day 2 minus Δd′ Day 1). Lastly, a multiple regression analysis used Day 1 PM_{10} concentration, Day 2

PM_{10} concentration, and urbanicity (proxy for chronic pollution exposure) to predict change in Approach bias (Δd′ Day 2 minus Δd′ Day 1).

Memory Arena

Training

The number of training runs needed to reach the learning criterion (70% accuracy on spatial & sequential placement of objects on two consecutive runs) indicated ability to learn the placement and sequence of objects. An independent samples T-test was used to calculate the difference between pollution groups for number of training runs taken to reach this training threshold. As there was no imposed time limit for each run, the same analysis was completed for time taken to complete the training phase to identify if any compensatory mechanism was being used to learn the sequence and location of objects.

Memory Tests

Spatial placement error was calculated once for each chosen object as the straight-line distance in pixels between the centre of the dropped location of the chosen object and the centre of the correct location of that object. Sequential accuracy was scored as correct if the chosen image had been presented just after the previously chosen image regardless of whether the latter had been correctly selected, i.e., if object 6 is chosen after object 5 this is marked as correct even if object 5 was not correct. Two mixed ANOVAs (between-group factor: pollution group; within-subjects factor: day of testing) were conducted on spatial error and sequential accuracy respectively.

Results

Emotional Discrimination Task

Face expression sensitivity (d′) between exposure groups

First, an ANOVA was conducted comparing stimuli intensity (1, 2, 3, 4), emotion expression (happy, fearful), and day of testing (Day 1, Day 2), and pollution exposure group (High PM_{10}, Low PM_{10}). A main effect of expression was identified [$F(1, 45) = 28.338$, $p < 0.001$, $\eta p^2 = 0.392$, $1\text{-}\beta = 0.999$], such that d′ was significantly higher for happy (mean d′ = 1.99, s.d. = 0.54) than fearful stimuli (mean d′ = 1.76, s.d. = 0.61); as expected, this implies that there was a tendency to approach happy faces and avoid fearful faces, confirming the concept of Approach bias. Mean d′ values were similar to those identified in Chapter 2 [happy (mean d′ = 2.00, s.d. = 0.44); fearful (mean d′ = 1.66, s.d. = 0.59)], replicating the underlying propensity to approach happy rather than fearful expressions, suggesting that participants performed similarly in the perceptual component of the task across both studies.

There was a main effect of intensity [$F(2.479, 109.085) = 247.035$, $p < 0.001$, $\eta p^2 = 0.849$, $1\text{-}\beta = 1$], such that intensity 1 was the least easily distinguished (mean d′ = 0.78, s.d. = 0.41); followed by intensity 2 (mean d′ = 1.54, s.d. = 0.51); intensity 3 (mean d′ = 2.38, s.d. = 0.82); and intensity 4 (mean d′ = 2.81, s.d. = 0.76), $p < 0.001$ for all intercomparisons. (See Figure 3.2).

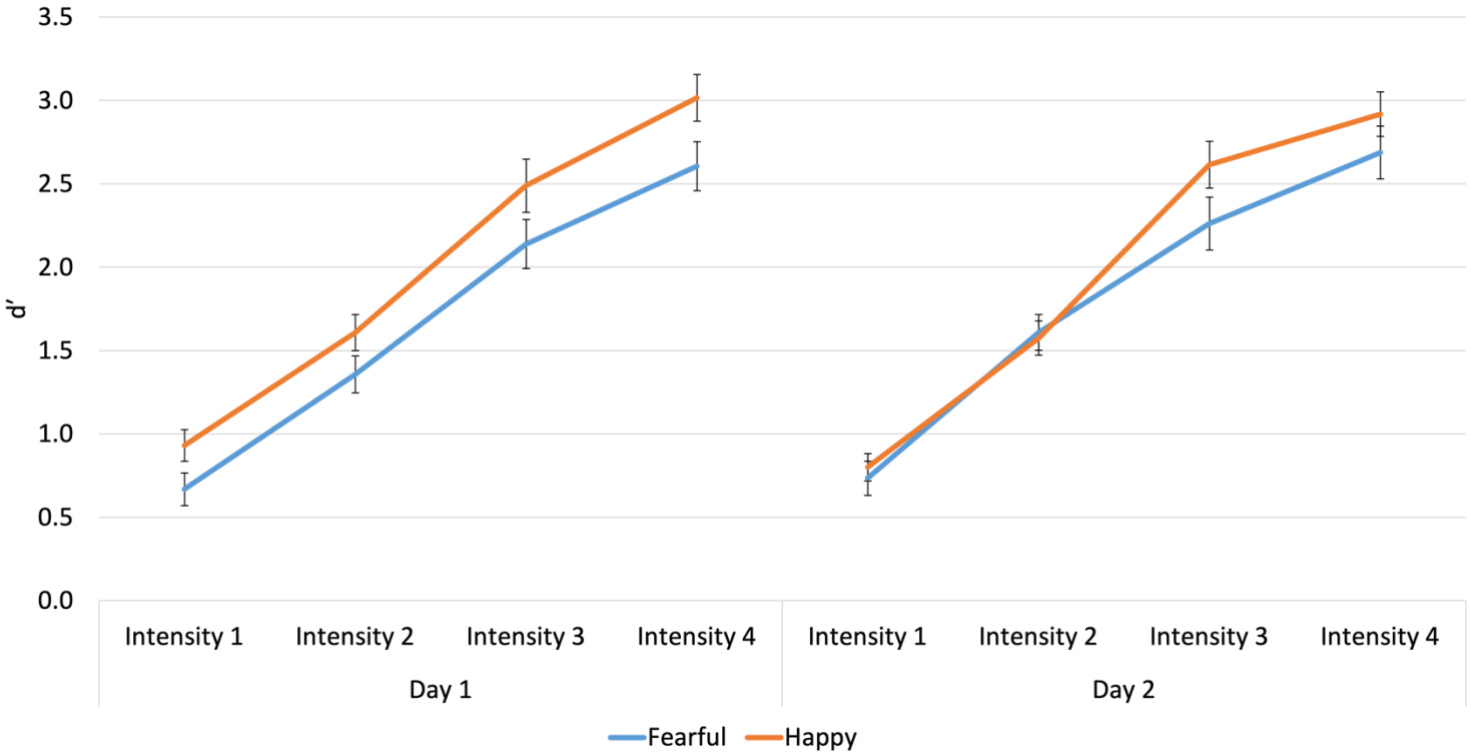
There were no significant interactions between air pollution exposure condition and stimuli intensity: [intensity*condition: $F(3, 132) = 1.007$, $p = 0.392$; day*intensity*condition: $F < 1$; day*expression*intensity*condition: $F(3, 132) = 1.905$, $p = 0.132$]. As there were no interactions between emotional intensity and condition, d′ was collapsed into emotion expression, regardless of intensity for the remaining analyses.

As in Chapter 2, the prediction was that d′ should be greater for happy than for fearful face targets reflecting a positive affect Approach bias and that this bias might be negatively affected on Day 2 by high pollution exposure on Day 1. Indeed, the 2x2x2 ANOVA of d′ scores showed a significant 3-way interaction of pollution condition, target expression, and day of testing [$F(1, 44) = 6.077$, $p = 0.018$, $\eta p^2 = 0.121$, $1\text{-}\beta = 0.674$]. To investigate and simplify, a Δd′ score was calculated for each participant and Day by subtracting d′ fearful from d′ happy. (d′ score for each target expression and Day are shown for each pollution group in Table 3.2). Although a 2x2 ANOVA (pollution group x day) showed no significant main effect of pollution group on Δd′ [$F(1,$

44) = 0.017, p = 0.896], a significant interaction between pollution group and day [F(1, 44) = 6.077, p = 0.018, ηp^2 = 0.121, $1\text{-}\beta$ = 0.674] was identified. Δd′ did not differ between air pollution groups on Day 1 [t(44) = -1.700, p = 0.096; Low PM (mean Δd′ = 0.13, s.d. = 0.33); High PM (mean Δd′ = 0.32, s.d. = 0.42)], or differ on Day 2 [t(44) = 1.950, p = 0.058); Low PM (mean Δd′ = 0.20, s.d. = 0.30); High PM (mean Δd′ = 0.0, s.d. = 0.42)]. (See Figure 3.3A). However, the interaction between day and pollution condition indicated an increase in sensitivity towards happy targets on Day 2 compared to Day 1 in the low PM exposure group, mimicking the results of Chapter 2 for the Clean Air condition. Whilst typical approach-avoidance biases were seen in Day 1 in the high PM exposure group (Day 1 Δd′ = 0.32), there was no bias for happy over fearful targets on the second day for these participants (Day 2 Δd′ = 0). This indicated that despite showing expected propensities to approach happy stimuli in those exposed to higher PM concentrations on Day 1, they showed no such bias 24 hours later.

Figure 3.2

Line Graph showing Sensitivity (d') for each Intensity of Stimuli across both Testing Days

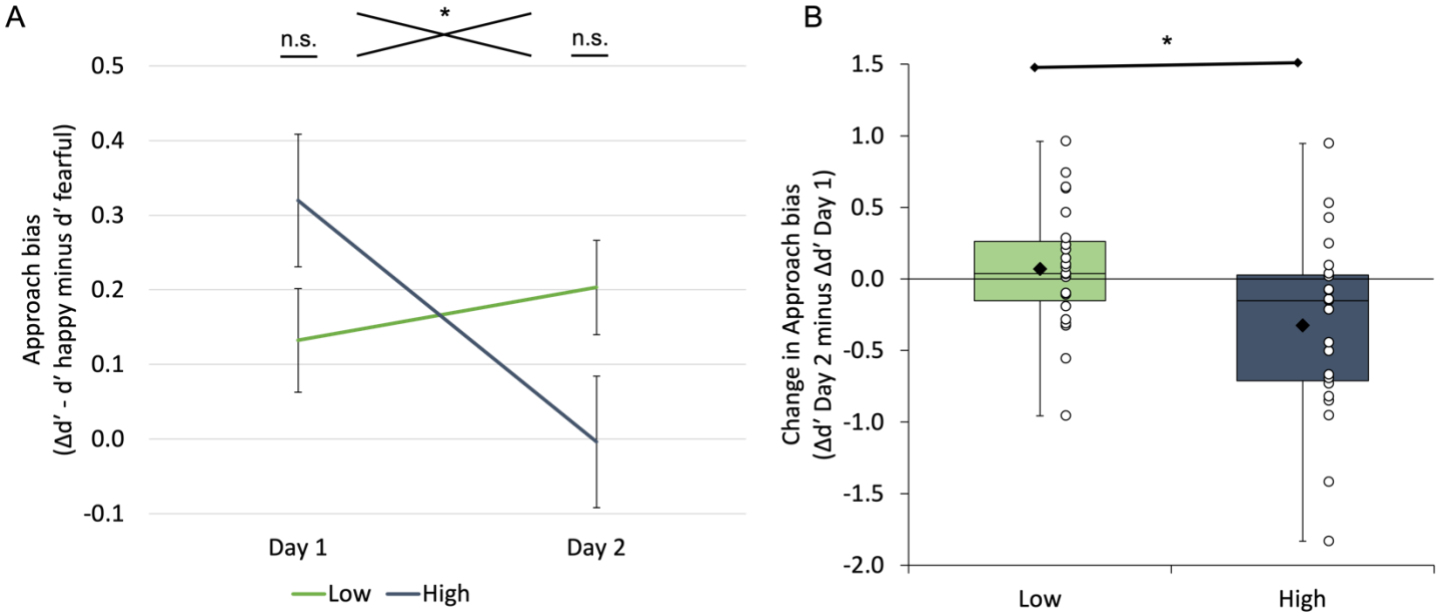


Note. There was a main effect of expression intensity; participants were more sensitive to intensity 4 expressions than intensity 3, with the same true for all further comparisons. There was also a main effect of expression; sensitivity to happy faces was significantly higher than fearful

Following this, Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1) was compared between pollution exposure groups. The Low pollution group showed a greater Change in Approach bias (mean change = 0.07, s.d. = 0.44), implying a shift towards higher sensitivity to happy compared to fearful faces on day 2 compared to day 1. This differed for the High pollution group which showed the opposite effect [mean change = -0.32, s.d. = 0.63; $t(44) = 2.465$, $p = 0.018$]. (See Figure 3.3B).

Figure 3.3

A: *Line Graph showing Approach bias [Δd′ (d′ happy minus d′ fearful)] and* **B**: *Boxplot showing Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1) for both Pollution Conditions*



Note. **A**: Significant interaction between pollution group and testing day. Points indicate mean values and error bars indicate standard error. Higher values indicate increased sensitivity to happy compared to fearful target expressions. **B**: The High pollution group shows a significant change in expression sensitivity in favour of fearful compared to happy stimuli from Day 1 to Day 2 in comparison to the Low pollution group. Circles indicate individual participant Change in Approach bias, diamonds indicate group means

As overall expression sensitivity (d′) was not significantly different across day 1 and 2, the differences identified between d′ for different expressions between days are likely due to pollution exposure group. The different shift in d′ across testing days between conditions implies that those in the High PM group increased sensitivity to fearful stimuli on the second day of testing compared to the first, whilst the opposite was true for the Low PM group. Overall, this result mimics that of the experimental exposure conditions in Chapter 2, again suggesting that 24 hours after exposure

to higher concentrations of particulate matter, participants show a bias towards negative-affective stimuli in comparison to their baseline performance, whilst those exposed to lower concentrations show an expected shift in bias towards positive-affective stimuli after the same delay period.

As participants were also exposed to varying levels of pollution on the commute to the second day of testing, individual average PM_{10} concentrations on the second commute were added into the 2x2 analysis as a covariate to control for this as potentially driving the significant effects identified. Similarly, as participant Body-Mass Index (BMI) was significantly higher in the High pollution group compared to the Low pollution group, BMI was also added into the 2x2 analysis as a covariate. The inclusion of second day PM_{10} concentrations and BMI as covariates did not alter any of the reported results. The interaction between day of testing and pollution group on Approach bias ($\Delta d'$) remained significant [$F(1, 42) = 5.212$, $p = 0.028$, $\eta p^2 = 0.110$, $1\text{-}\beta = 0.607$]; all other main effects and interactions were non-significant (*F-values* < 1). This implied that PM_{10} concentration on day 2 and participant BMI were not mediating factors in the identified effect of Day 1 pollution concentration on Change in Approach bias.

Baseline (Day 1) Approach bias was somewhat similar between the Low pollution group (mean $\Delta d' = 0.13$, s.d. = 0.33) in the present natural-experimental study and the experimental Clean Air group from Chapter 2 [mean $\Delta d' = 0.20$, s.d. = 0.41; $t(62) = 0.649$, $p = 0.519$]. Whilst Approach bias was higher in the High pollution group (mean $\Delta d' = 0.32$, s.d. = 0.42) of the current study compared to the Candle manipulation group (mean $\Delta d' = 0.15$, s.d. = 0.42), this difference was non-significant [$t(48) = -1.413$, $p = 0.164$].

Approach bias appeared lower in the High pollution group (mean $\Delta d' = 0.00$, s.d. = 0.41) in the present study compared to the Candle manipulation group (mean $\Delta d' = 0.10$, s.d. = 0.35) 24 hours later (Testing Day 2), although again this difference was non-significant [$t(48) = 0.987$, $p = 0.328$]. Day 2 Approach bias was significantly higher in the experimental Clean Air group (mean $\Delta d' = 0.42$, s.d. = 0.37) than the Low pollution group (mean $\Delta d' = 0.20$, s.d. = 0.30) in the current study [$t(62) = 2.340$, $p = 0.023$]. This difference may be explained by the fact that the Low exposure group are not a clean air cohort as they were exposed to higher average PM_{10} concentrations than the Clean Air experimental group.

Hence, the Change in Approach bias between days with the experimental Clean Air group showing a greater shift towards positive-affective Approach bias between days (mean change = 0.22, s.d. = 0.46) compared to a more conservative positive shift in the Low natural-experimental

pollution group (mean change = 0.07, s.d. = 0.44). The High natural-experimental pollution group showed a greater negative shift of Approach bias (mean change = -0.32, s.d. = 0.63) compared to the Candle manipulation group (mean change = -0.05, s.d. = 0.44).

Table 3.2

Mean Performance [Hit Rate, False Alarm Rate, d', Approach bias (Δd'), and Change in Approach bias] across Stimuli Expression and Testing Day for both Pollution Conditions

Metric Description			Low PM_{10} Exposure	High PM_{10} Exposure
Hit Rate	Day 1	Happy	79.1% (*8.2%*)	83.3% (*8.8%*)
		Fearful	85.0% (*6.3%*)	80.2% (*8.5%*)
	Day 2	Happy	82.2% (*5.8%*)	80.2% (*8.1%*)
		Fearful	86.3% (*7.6%*)	86.2% (*5.4%*)
False Alarm Rate	Day 1	Happy	25.7% (*16.0%*)	17.5% (*7.0%*)
		Fearful	36.8% (*14.5%*)	31.6% (*14.8%*)
	Day 2	Happy	26.8% (*14.5%*)	19.7% (*6.2%*)
		Fearful	40.7% (*19.8%*)	28.2% (*12.8%*)
Expression sensitivity - d′	Day 1	Happy	1.57 (*0.54*)	1.85 (*0.36*)
		Fearful	1.43 (*0.45*)	1.53 (*0.60*)
	Day 2	Happy	1.62 (*0.48*)	1.75 (*0.35*)
		Fearful	1.42 (*0.61*)	1.75 (*0.50*)
Approach bias (Δd′ – d′ happy minus d′ fearful)		Day 1	0.13 (*0.33*)	0.32 (*0.42*)
		Day 2	0.20 (*0.30*)	0.00 (*0.41*)
Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1)			0.07 (*0.44*)	-0.32 (*0.63*)

Note. Standard deviation in parenthesis

Approach bias (Δd′) regression analyses

Following the same pattern of results for both the current study and the study outlined in Chapter 2, data from both studies was pooled to conduct linear regression analyses of the predictor, Day 1 average PM_{10} concentration, on the criterion, Approach bias, indexed by Δd′ (d′ happy minus d′ fearful).

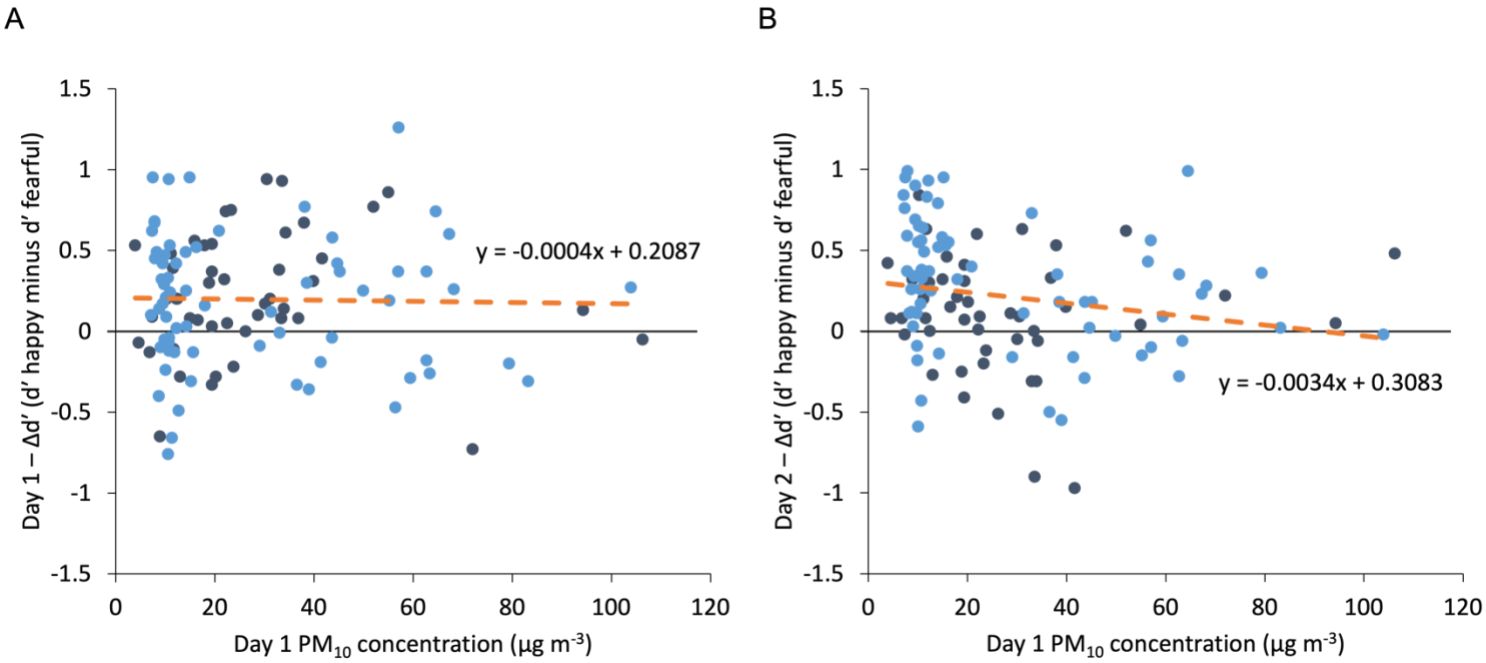
A simple linear regression was used to examine the relationship between Day 1 PM_{10} concentration and approach-avoidance bias on the second day of testing (24 hours after exposure). The regression equation produced a good fit with the data (R^2 = 0.038), indicating that, as hypothesised, PM_{10} concentration was a good predictor of approach-avoidance bias 24 hours after exposure (On testing Day 2), $F(1, 112) = 4.395$, $p = 0.039$. There was a significant negative relationship between PM_{10} concentration and Δd′ ($T = -2.094$, $p = 0.039$), with Δd′ decreasing with increases in PM_{10} concentration. The model predicted that a ten unit increase in PM_{10} concentration (μg m^{-3}) would result in a decrease in Δd′ of 0.03. (See Figure 3.4B). This result indicated that exposure to higher PM_{10} concentrations predicted a reduction in Approach bias.

Another regression analysis was conducted to examine the relationship between PM_{10} concentration and Day 1 Approach bias. As expected based on the group comparisons, no significant relationship was identified between the variables [$F(1, 112) = 0.055$, $p = 0.815$]. This indicated that PM_{10} exposure on Day 1 was not related to Approach bias on Day 1. (See Figure 3.4A).

A final simple regression analysis showed no significant relationship between Change in Approach bias between days (Δd′ Day 2 minus Δd′ Day 1) and Day 1 PM_{10} concentrations [$F(1, 112) = 1.901$, $p = 0.171$]. This was contrary to expectations, as group analyses for both studies highlighted a lower change in Approach bias in High pollution / Candle manipulation groups compared to Low pollution / Clean Air groups.

Figure 3.4

Scatterplots showing Day 1 Average PM_{10} Concentrations and Approach bias (Δd') on **A**: *Day 1 and* **B**: *Day 2*



Note. Circles indicate individual participants; light blue indicates participants in the current natural-experimental exposure study; dark blue indicates participants from the manipulation experiment in Chapter 2; dashed lines indicate linear line of best fit. Regression equations are included on each graph. **A**: No significant relationship between Day 1 PM_{10} Concentration and Approach bias. **B**: Significant relationship such that Approach bias was lower for participants 24 hours after exposure to higher PM_{10} concentrations

As the simple regression investigating the relationship between Day 1 PM_{10} concentration and change in Approach bias was non-significant contrary to expectations, a multiple regression analysis was conducted to determine the predictive value of PM_{10} concentration on Day 1, Day 2, and urbanicity score (a proxy for chronic pollution exposure) on Change in Approach bias between days (Δd′ Day 2 minus Δd′ Day 1). This was conducted to examine the role of potential confounding factors Day 2 PM_{10} concentration and chronic pollution exposure on Change in Approach bias, possibly explaining the non-significant result of the simple regression.

All variables were entered into the model and variables with the least predictive power were removed with each iteration. For each variable, the mean, standard deviation, and range of scores were recorded. (See Table 3.3). No significant relationships were identified between predictors. (See Table 3.4). All variables together accounted for 2.6% of the variance of Change

in approach-avoidance bias in the sample. Neither Day 1 PM_{10} concentration (β = -0.131, p = 0.167), Day 2 PM_{10} concentration (β = -0.024, p = 0.801), or urbanicity (β = -0.091, p = 0.337) were significant predictors of Change in approach-avoidance bias. The beta values indicate that despite the non-significant results, Day 1 PM_{10} concentration had the greatest predictive power to explain Change in Approach bias.

Table 3.3

Means and Standard Deviations of all Variables entered in the Regression Analysis

Variable	*M*	*SD*	Range
Average PM_{10} concentration (μg m^{-3}) - Day 1	27.84	22.61	3.94 to 106.27
Average PM_{10} concentration (μg m^{-3}) - Day 2	30.78	25.58	3.68 to 135.45
Urbanicity	5.02	1.27	1.24 to 6.95
Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1)	0.016	0.523	-1.83 to 1.26

Note. '*M*' indicates mean, '*SD*' indicates standard deviation

Table 3.4

Intercorrelations between Change in Approach bias and all Predictor Variables in the Regression Analysis

Variable	1	2	3
1. Change in Approach bias (Δd′ Day 2 minus Δd′ Day 1)	—	—	—
2. Average PM_{10} concentration (μg m^{-3}) - Day 1	-0.129	—	—
3. Average PM_{10} concentration (μg m^{-3}) - Day 2	-0.033	0.053	—
4. Urbanicity	-0.087	-0.035	0.022

Note. N = 114. No correlation reached statistical significance at α = 0.05 level

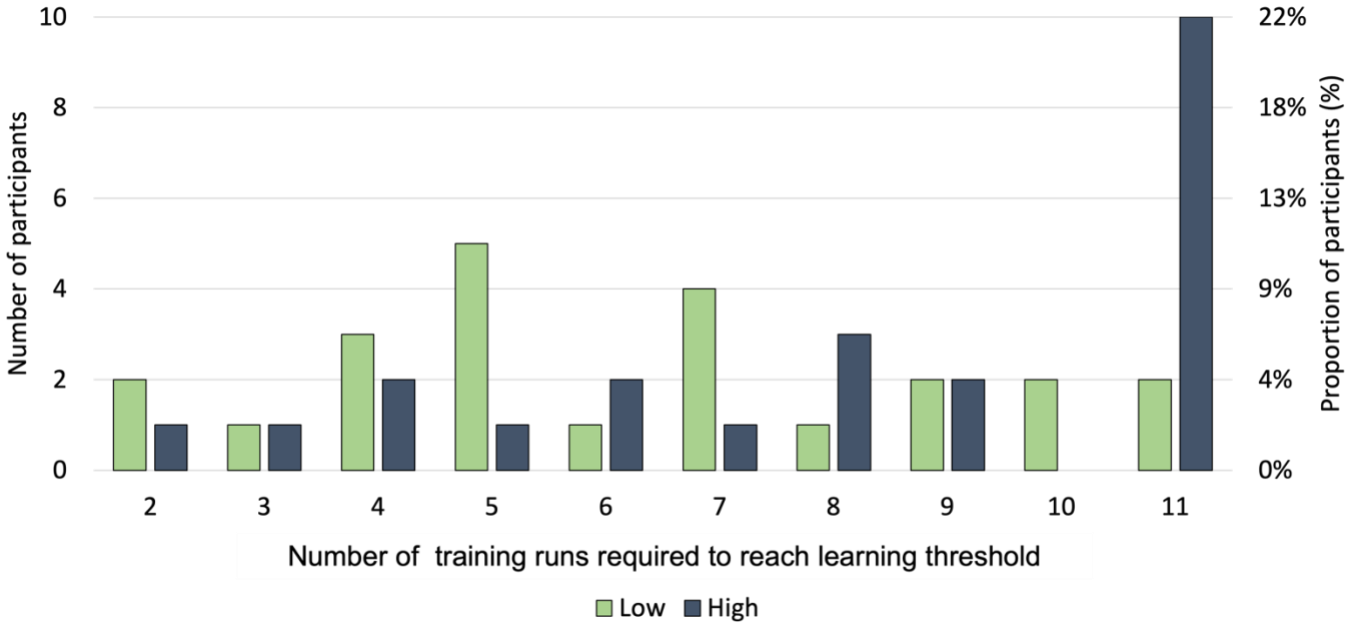
These results imply that for both experiments, exposure to higher PM_{10} concentrations on the first testing day is related to a lower sensitivity to happy face expressions (compared to fearful) 24 hours later regardless of baseline performance.

Memory Arena

The training phase was analysed to identify differences in learning between pollution exposure groups. The number of runs taken to learn the sequence and location of objects (learning criterion: 70% correct) was significantly higher in the High pollution group (mean = 8.22 runs, s.d. = 3.03) compared to the Low pollution group [mean = 6.35 runs, s.d. = 2.72; $t(44) = -2.201$, $p = 0.033$]. (See Figure 3.5). This implies that a short exposure to higher PM_{10} concentrations negatively impacts immediate ability to learn the sequence and location of 20 objects in comparison to lower concentrations during commuting. This was also true for time taken to complete the training phase, with the High pollution group taking significantly longer (mean = 27.04 minutes, s.d. = 9.47) than the Low pollution group [mean = 19.94 minutes, s.d. = 6.88; $t(44) = -2.910$, $p = 0.006$]. Indeed, there was a strong positive correlation between number of training runs and time on the training phase ($r = 0.861$, $n = 46$, $p < 0.001$), implying that compensatory mechanisms did not influence this difference in encoding ability.

Figure 3.5

Number and Percentage of Participants requiring n *Training runs to reach the Learning Threshold in both Exposure Conditions*



Note. Learning threshold was 70% accuracy of spatial and sequential object placement across two consecutive runs. The Low pollution group shows a normal distribution, whilst the High pollution group shows a negative skew; a greater proportion of participants took more training runs to reach the learning threshold compared to the Low pollution group.

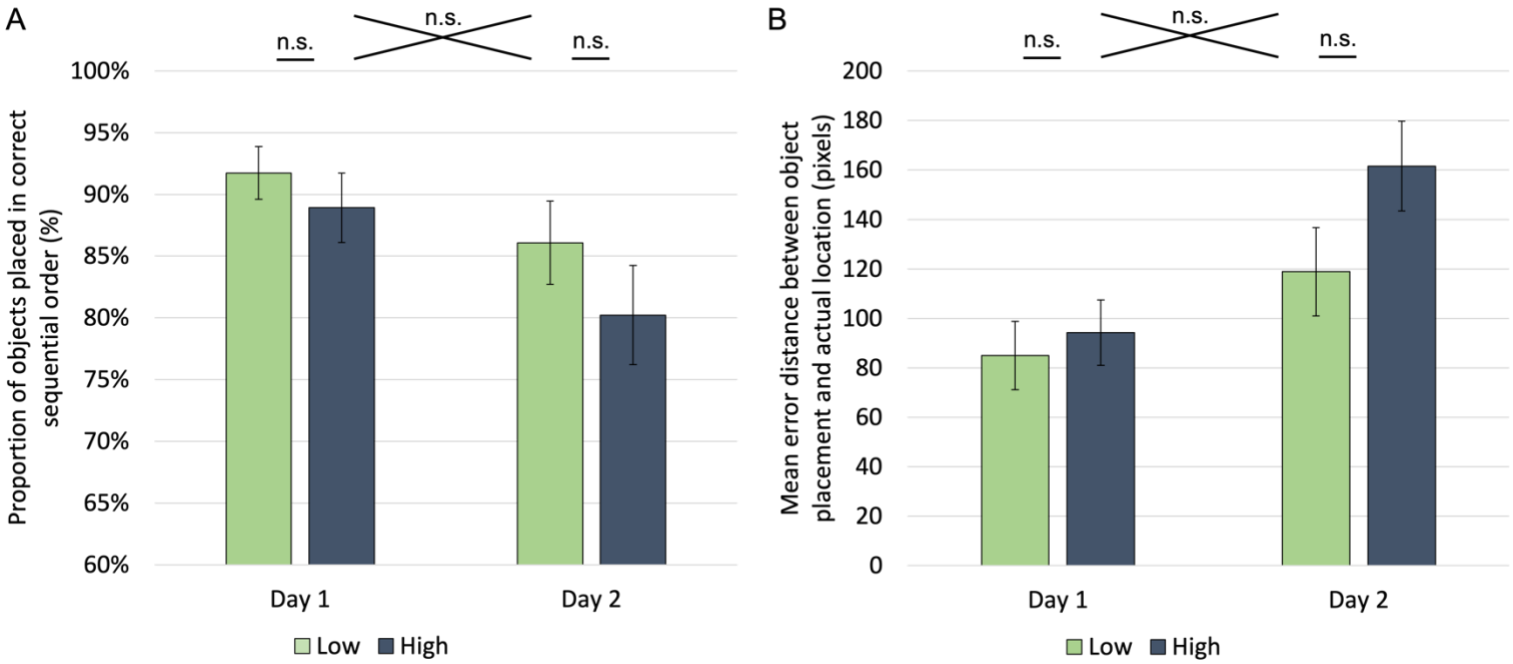
Participant performance for object sequence recall was analysed for each pollution group across the two testing days. A 2x2 mixed ANOVA identified a significant main effect of day such that participants had higher correct sequence placement on the first day (mean = 90.3%, s.d. = 11.71) compared to the second day [mean = 83.15%, s.d. = 17.46; $F(1, 44) = 12.436$, $p < 0.001$, $\eta p^2 = 0.220$, $1\text{-}\beta = 0.932$]. This was expected, as participants were instructed not to actively reconsolidate between sessions. Importantly, no main effect of condition or interaction was identified [condition: $F(1, 44) = 1.258$, $p = 0.268$; interaction: $F < 1$], implying that exposure to pollution did not affect sequence recall ability or the change in sequence recall ability between test days. (See Figure 3.6A).

Participant recall error distances between object placement location and true object location were analysed for both pollution groups across the two testing days. A 2x2 mixed ANOVA identified a significant main effect of day such that participants had a lower mean error between object placement location and actual object position on Day 1 (mean = 90 pixels, s.d. = 63) compared to Day 2 [mean = 140 pixels, s.d. = 86; $F(1, 44) = 26.992$, $p < 0.001$, $\eta p^2 = 0.380$, $1\text{-}\beta = 0.999$]. In line with the results on sequence recall, no main effect of condition or interaction was identified [condition: $F(1, 44) = 1.736$, $p = 0.194$; interaction: $F(1, 44) = 2.954$, $p = 0.093$], implying that exposure to pollution did not affect overall object placement error or a change in object placement error between test days. (See Figure 3.6B).

As seen in the candle manipulation study, these results also suggest that exposure to high concentrations of particulate matter do not impact episodic memory ability, specifically memory for sequences and object locations. However, the results imply that those exposed to higher concentrations of PM_{10} during their commute encountered more difficulty in learning from feedback given during training runs.

Figure 3.6

Bar Charts showing **A**: *Mean Object Sequence Accuracy and* **B**: *Mean Object Location Error Distance for both Exposure Conditions*



Note. **A**: Significant main effect of testing day identified but no other main effects or interactions. Columns indicate mean proportion correct (%) and error bars indicate standard error. **B**: Significant main effect of testing day identified but no other main effects or interactions. Columns indicate mean error values (pixels) and error bars indicate standard error
n.s. indicates non-significant

To further explore the significant differences in time and training runs taken to reach the training criterion, data was pooled between the current study and Chapter 2 for regression analyses. A simple linear regression analysis of the predictor, Day 1 average PM_{10} concentration, on the criterion, number of training runs was conducted. There was no significant relationship between the variables [$F(1, 112) = 0.659$, $p = 0.419$], indicating that pollution exposure on Day 1 was not related to number of training runs needed to reach the criterion. This was the same for time taken to reach the training criterion [$F(1, 112) = 0.167$, $p = 0.684$].

These analyses suggest that despite the High PM_{10} group in the current study taking significantly more time and training runs to complete the training phase compared to the Low PM_{10} group; this was not universal across both studies.

Air Quality Measures

Particulate Matter Concentrations

PM_1, $PM_{2.5}$, and PM_{10} concentrations were collected at 1 second intervals from when participants started their car for their commute (Average journey time 27 minutes), until they stopped the car when parked at the University of Birmingham. These data were then averaged across each commute to give average PM concentrations for each participant for each commute. Following a median split of the data according to average PM_{10} concentrations for the first commute, three separate T-tests were conducted to compare average concentrations of PM_1, $PM_{2.5}$, and PM_{10} between the resultant 'Low' and 'High' pollution groups. Results of these T-tests were all significant, indicating that average PM_1 concentrations were significantly higher in the 'High' pollution group (mean = 14.18 μg m^{-3}, s.d. = 12.88) compared to the 'Low' group [mean = 5.20 μg m^{-3}, s.d. = 3.34; $t(44) = -3.235$, $p = 0.002$]; the same for $PM_{2.5}$ concentrations, [High: mean = 17.39 μg m^{-3}, s.d. = 14.22; Low: mean = 6.47 μg m^{-3}, s.d. = 3.96; $t(44) = -3.549$, $p < 0.001$]; and PM_{10} concentrations, [High: mean = 40.99 μg m^{-3}, s.d. = 22.03; Low: mean = 13.83 μg m^{-3}, s.d. = 5.30; $t(44) = -5.748$, $p < 0.001$].

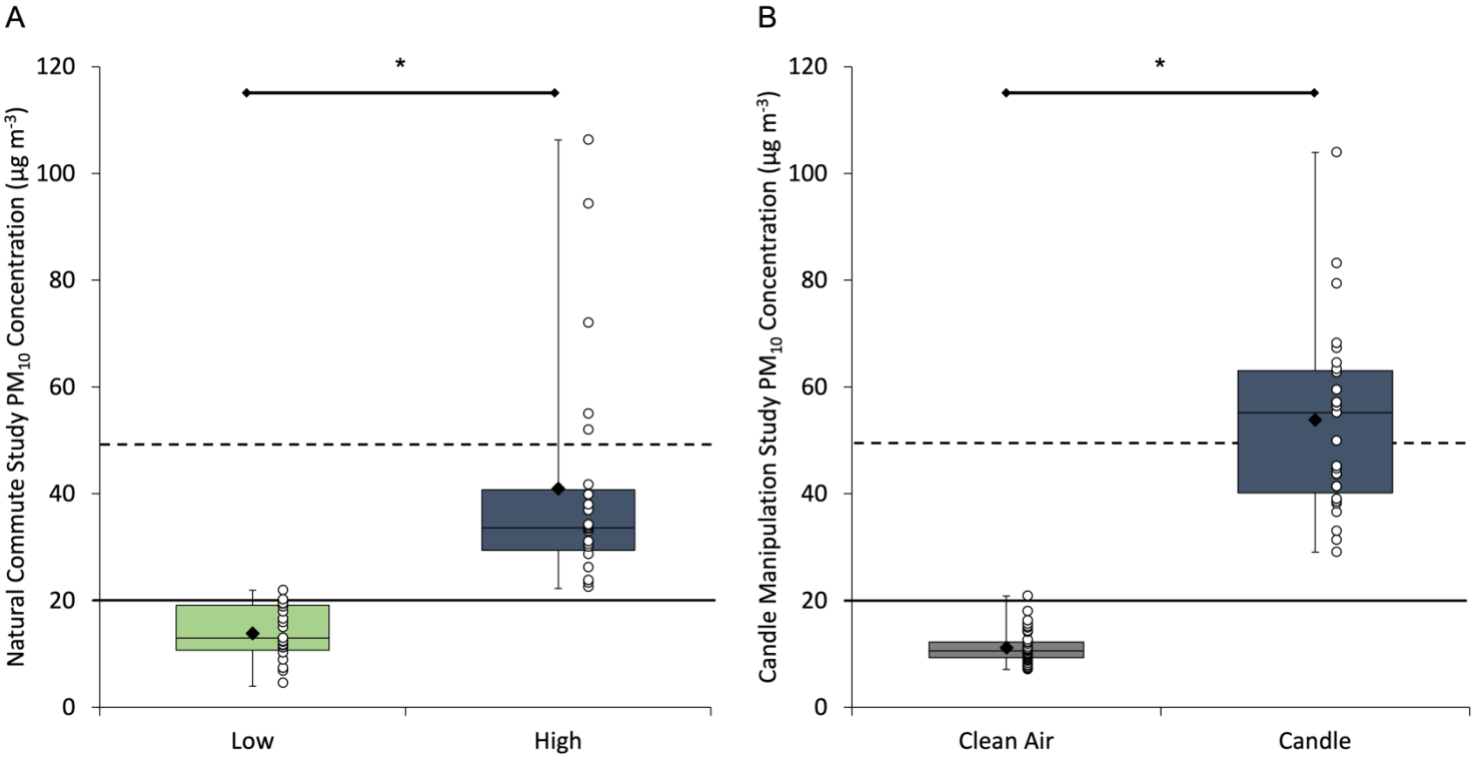
Lastly, a 2x2 between-subjects ANOVA with experimental study (Candle Manipulation, Natural Commute) and pollution group (Low PM, High PM) was conducted to compare the concentrations of pollutants across the studies as the outcomes were similar. There was a significant main effect of pollution group [$F(1, 110) = 184.705$, $p < 0.001$, $\eta p^2 = 0.627$, $1\text{-}\beta = 1$], such that the low PM groups (Clean Air and Low pollution ;mean = 12.13 μg m^{-3}, s.d. = 4.16) were exposed to lower concentrations than the high PM groups (Candle and High pollution; mean = 47.95 μg m^{-3}, s.d. = 20.54). There was a significant interaction between pollution group and study [$F(1, 110) = 9.148$, $p = 0.003$, $\eta p^2 = 0.077$, $1\text{-}\beta = 0.850$] as whilst PM_{10} concentration in the candle manipulation study low pollution (Clean Air) condition (mean = 11.18 μg m^{-3}, s.d. = 3.04) was significantly lower than the natural commute study Low pollution group [mean = 13.83 μg m^{-3}, s.d. = 5.30; $t(62) = 2.548$, $p = 0.013$], PM_{10} concentrations were significantly higher in the candle manipulation study high pollution (Candle) condition (mean = 53.88 μg m^{-3}, s.d. = 17.46) compared to the natural commute study High pollution group [mean = 40.99 μg m^{-3}, s.d. = 22.03; $t(48) = -2.309$, $p = 0.025$].

Whilst there was a significant main effect of experimental study [$F(1, 110) = 3.975$, $p = 0.049$, $\eta p^2 = 0.035$, $1\text{-}\beta = 0.507$], such that average concentrations were higher in the candle

manipulation study (mean = 28.14 μg m^{-3}, s.d. = 23.81) than the present commute study (mean = 27.41 μg m^{-3}, s.d. = 20.96), this effect was marginal (p = 0.049). (See Figure 3.7).

Figure 3.7

Boxplots indicating Mean PM_{10} Concentrations in the **A**: *Current Study and* **B**: *Experimental Manipulation Study in Chapter 2*



Note. Lower concentrations indicate cleaner air. White circles indicate individual participants, black diamonds indicate group means. Dashed lines indicate World Health Organization average annual concentration limits with solid lines indicating average 24-hour concentration limits

This result suggests that extinguishing a candle in the experimental manipulation study increased PM_{10} concentrations significantly more than average concentrations experienced during participant commutes in the present study. The marginal significant effect of experimental study suggests comparisons could still be made between the experimental studies, and evidence highlighting similar baseline cognitive performance in both experimental studies provides a strong argument for such comparisons.

Discussion

In this study, participants' commutes were analysed to determine if they were exposed to high or low concentrations of particulate matter, as a proxy for all air traffic-related air pollutants (TRAP). Immediately following exposure during commuting, participants completed an episodic memory task and a Go/No-go task with a social cognition component. After 24 hours these were tested once more. Those exposed to high PM_{10} concentrations during the commute showed a shift of Approach bias — i.e., expression sensitivity towards negative-affective stimuli — after a 24-hour period compared to the Low pollution group. Those exposed to high PM concentrations during Day 1 commutes took longer to learn the sequential order and spatial location of 20 objects compared to those in the Low pollution group. Performance on recalling the sequence and location of objects was the same for both High and Low PM groups on both testing days.

The Approach bias interaction between testing day and pollution exposure group replicates the results of the study outlined in Chapter 2, showing a decline in Approach bias between Day 1 and Day 2 for those exposed to higher pollution concentrations during their commute. This replication of results strongly supports a general time-delayed effect of air pollution on Approach bias and is the first report of such an effect. The time-delay suggests inflammation is a reasonable mechanistic hypothesis to explain the Change in Approach bias as day 1 PM exposure did not show significant differences between Approach bias on Day 1, but the High pollution group showed a sensitivity shift in Approach bias towards fearful expressions across days, with the opposite being true for the Low pollution group.

When data was pooled between Chapters 2 and 3 for regression analyses, Approach bias 24 hours after exposure (Day 2) was significantly predicted by Day 1 PM_{10} exposure concentration. However, both immediate (Day 1) Approach bias and Change in Approach bias between Day 1 and Day 2 was not predicted by PM_{10} concentration on Day 1. These results discount the possibility that the identified effect of AP on task performance is due to practice effects as was left open as an explanation in Chapter 2. If task practice induced a reduction in executive control, PM_{10} concentration would predict change in Approach bias across days. As only Day 2 Approach biases were predicted by Day 1 PM_{10} exposure concentrations, it is reasonable to assume that effects are due to changes in top-down control processing. Prepotent emotional schemas are strategically utilised to guide attention during goal-oriented tasks (Mohanty and Sussman, 2013), in this case an Approach bias towards positive-affective stimuli. 24 hours after a high pollution exposure

episode, neurotransmission responsible for the inclusion of these schemas may be attenuated, leading to a lack of access to the prepotent information that normally drives Approach bias behaviour. Essentially, inflammation appears to cause a reduction in sensitivity to stimuli-relevant emotional information; in this case, high concentrations of air pollution may have caused a reduction in sensitivity to positive-affective stimuli.

Taking all the results into account, it is still reasonable to suggest executive functioning alone could be impaired after air pollution exposure, but these effects were confounded due to using emotion as a target classifier. Evidence suggests that the behavioural responses to an emotional adaptation of the classic Go/No-go task, similar to the present study, closely match that of the original non-emotional version (Schulz et al., 2007). In future, using a different executive function paradigm would enable investigation into the reliance of emotional and/or face stimuli on this effect. There are two avenues for further investigation here to consider; firstly, would the results be the same if positive and negative-affective stimuli were not human face expressions, for example, a birthday cake (positive-affective) compared to a firearm (negative-affective). Alternatively, the use of a separate executive function paradigm would allow investigation into whether the identified effect is only emotion-relevant or indicates a generalised dysfunction of executive control.

Interestingly, the results on the Memory Arena differed to those of Chapter 2. In the present study, participants in the High PM_{10} group took more training runs to form object-location and object associations to a learning criterion (70% accuracy) compared to the Low pollution group, implying an immediate impact of air pollution exposure on spatiotemporal encoding ability. The difference between encoding ability mediated by pollution exposure across the two studies may imply that encoding ability is attenuated by air pollution from alternate pollutant-species than PM. Importantly, this deficit cannot be explained through the inflammation hypothesis as the difference was identified immediately following commuting rather than after the 24-hour delay seen in the Emotional Discrimination Task.

Hypoxia may be an explanation for the immediate nature of this effect. That is, participants exposed to higher PM_{10} concentrations (but also other TRAP pollutants including oxygenated-species) during commute struggled to encode object sequence and location into memory compared to the low exposure group due to system-wide deoxygenation. It is reasonable that pollution exposure could cause immediate cognitive effects based on EEG evidence of immediate and fast-

acting (within 30 minutes) changes in resting state activity following pollution exposure (Crüts et al., 2008; Naseri et al., 2019) as well as evidence that global cognitive functioning is immediately impacted following commute (Shehab and Pope, 2019).

Under ambient conditions, blood Carboyxhaemoglobin (COHb) levels in the human body are not expected to exceed 5% (Gupta, 2015, p. 271). Evidence shows that after exposure to high concentrations of CO (9600 ppm for ~ 5 minutes), COHb levels rise to an average of 15.3% (s.d. 2.81). Interestingly, COHb concentrations were positively correlated with change in brain blood flow, such that higher COHb percentages were related to an increase in brain blood flow compared to baseline (pre-exposure) measures. This indicated a compensatory mechanism to increase the amount of blood to the brain to ensure sufficient oxygenation levels (Benignus et al., 1992). Whilst this clearly shows the impact of CO exposure on brain function, the CO concentrations used in the study were far beyond what was likely experienced during participant commute. However, more recent evidence confirms that even low-level (under 50 ppm) exposure to CO still shows changes using more sensitive and reliable imaging techniques (BOLD response measured during fMRI; Bendell et al., 2020). Another study exposed participants to 61 ± 24 ppm CO for ~ 2 hours and showed impairments on several cognitive tasks (Amitai et al., 1998). Whilst memory encoding was not specifically measured, recall ability was significantly reduced in the CO exposed participants compared to a matched control group. This may indicate a failure to encode information (as you cannot recall information which has not been encoded), as identified in the current study. A failure to encode during hypoxic conditions independent of pollution exposure has also been demonstrated (Nation et al., 2017), although again oxygen desaturation was higher than one might experience from TRAP.

There is somewhat mixed evidence as to average CO concentrations inside vehicles themselves, with concentrations > 50 ppm unlikely, however, it is clear that recorded in-vehicle concentrations are often much higher than fixed site monitors (El-Fadel and Abi-Esber, 2009). Given the available evidence, acute hypoxia is a plausible explanation for the identified effect of high TRAP exposure on encoding ability. In future, measuring COHb levels via pre- and post-exposure blood sampling would aid in confirming the mechanism of these findings.

A potential confounding factor of the Memory Arena was participants using self-initiated encoding strategies as opposed to an experimenter-instructed strategy. It is plausible that the identified effect may reflect individual differences in memory encoding ability based on strategy

(Kirchhoff, 2009), although this is statistically unlikely given the high percentage of participants in the high exposure group (~22%) taking 11 runs to complete the task training phase. (See Figure 3.5).

Despite the identified effect of air pollution exposure on encoding, the recall results were similar to that of the experimental exposures in Chapter 2 as there were no significant group differences in recall ability on both testing days. Despite participants in the High pollution group taking longer to complete the training compared to Low pollution, as in Chapter 2 memory traces for all participants were at the same level prior to recall i.e., 70% accuracy or above. In future, participants should be instructed to use the same encoding strategy, for example, associating object location and order with a story; and the removal of training runs to remove the influence of ceiling effects on recall.

The use of a portable PM sensor in place of reliance on FSMs is a strength of this study, as acute pollution episodes were measured for individual participants and highlighted large variability which would likely not be captured otherwise. However, one caveat of this methodology was that only Particulate Matter was measured in place of all TRAP pollutant-species, meaning direct extrapolation of findings to other components of TRAP is not possible. On the other hand, there is evidence that key TRAP pollutants are moderately correlated, particularly when pollutants arise from the exhaust (rather than brake wear or another source). However, the strength of such correlation varies across regions due to land-use differences (Xie et al., 2015) and so may not be applicable to Birmingham, UK, where data was collected. Acute exposure to TRAP was not measured prior to the first testing day; the results strongly suggest that exposure during commute on the day prior to the first testing session will have influenced Day 1results. However, there was no significant correlation between average Day 1 and Day 2 PM_{10} concentration during commute ($r = 0.255$, $n = 46$, $p = 0.087$), indicating that despite often taking the same route during driving, individual experienced concentrations varied between days and therefore would likely also vary from the day prior to testing. In future extended pre-testing exposures could be collected to identify if an average commuter exposure score better predicts the identified effects over previous day concentrations.

Whilst the time taken to commute was not significantly different between groups, Low pollution (mean = 28.48 minutes, s.d. 14.42), High pollution (mean = 25.22 minutes, s.d. = 12.29), it is worth noting that participants were exposed for an unstandardised amount of time. Similarly,

average PM_{10} concentration is likely higher for those with shorter commutes. A participant who travelled through 1 pollutant 'hot spot' in a 60-minute drive would have a lower average concentration score than a participant driving through the same 'hot spot' in a 20-minute drive assuming similar concentrations across the remainder of the drive. However, as stated, there were no significant differences between journey time for the low and high exposure groups. This query opens a question for future research as to whether longer exposure to lower concentrations or shorter exposure to higher concentrations may be more critical to cognitive dysfunction. A reasonable method to answer this query would be to manipulate driving time and location (low vs. high traffic or urban vs. rural) for participants (long high-pollution drive; short high-pollution drive; long low-pollution drive; short low-pollution drive).

To summarise, this Chapter builds strongly on results presented in Chapter 2 showing a decline in pro-social behaviour 24 hours after a high exposure event, and that this effect is also present following acute natural outdoor exposures. It remains unknown whether this outcome is specific to socio-emotional cognition or if it represents a generalised decline in executive functioning, which is addressed in Chapter 4. This Chapter also highlighted the possible role of air pollution exposure in episodic encoding dysfunction immediately following exposure. However, a simplified episodic memory task with instructions on encoding strategy and removal of training runs is needed to verify that results are not simply due to individual differences in encoding strategy.

The implications of these results on commuters are mixed: whilst the effect of high TRAP exposure on immediate encoding dysfunction may seem concerning, with no evidence of TRAP exposure causing issues in retention and retrieval of information, the risk to commuters is negligible. Similarly, there is no evidence of an immediate decline in attention or executive function, which would pose substantial risks during commuting itself. The identified delayed degradation of pro-social behaviour may similarly not pose a physical health risk but may explain why air pollution exposure is linked to both social withdrawal and aggressive behaviours (Kaldewaij et al., 2016). Both social withdrawal and aggression are related to the affective disorder, depression (Weightman et al., 2014; Dutton and Karakanta, 2013). Considering the significant effect of one high-exposure episode on social cognition 24 hours later, it may be that multiple exposures during the working week may lead to a cumulative effect of TRAP exposure on poor social behaviour, posing risks for degradation of mental health.

Chapter 4 – Acute Diesel Exhaust Exposure causes Delayed reduction in Cognitive Control, but Episodic Memory remains intact

Author contributions

The following chapter is a manuscript submitted for review as part of collaborative work with Professor Jane Raymond, Professor Rob MacKenzie, Professor Kimron Shapiro, Professor Gordon McFiggans, Dr Rami Alfarra, and Dr Juana Maria Delgado-Saborit. Data was collected by TF (Author of thesis) with support from JMDS and RA. TF analysed the data with support from JR. JR, ARMK, KS, and GM contributed to the experimental design and interpretation. JR, ARMK, KS, GM, and JMDS secured funding for the study. At the time of thesis submission, TF prepared the manuscript and created the figures. JR, KS, ARMK, JMDS, and GM provided feedback during manuscript preparation.

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Additional analysis of interest follows the discussion of this previously prepared manuscript and is marked with an asterisk (*).

Abstract

Urban residents are frequently exposed to high levels of traffic-derived air pollution for short time periods, often (but not exclusively) during commuting. Although chronic air pollution exposure and health effects, including neurological effects on children and older adults, are known to be correlated, causal effects of acute pollution exposure on brain function in healthy young adults remain sparsely investigated. Neuroinflammatory accounts suggest effects could be delayed by several hours and could affect attention, especially in social contexts. Using a controlled atmosphere chamber, 81 healthy young adults were exposed to either diluted diesel exhaust (equivalent to polluted roadside environments) or clean air for one hour. Half of each group immediately completed a selective attention task to assess cognitive control; remaining participants completed the task after a 4-hour delay. Cognitive control over selective visual attention was significantly poorer after diesel versus clean air exposure for those in the delay but not immediate test condition, consistent with an inflammatory basis for this acute negative effect of air pollution on cognition. These findings provide the first experimental evidence that acute diesel exposure, comparable to polluted city streets, causes a negative effect on cognitive control several hours later. These findings may explain commuter mental fatigue and support clean-air initiatives.

These results support the notion presented in Chapters 2 and 3 that executive function alone is impacted by air pollution exposure after a delay period, albeit 4- instead of 24 hours as described in the previous results. Further investigation is required to determine if the results identified in the present study are only due to the super-distracting nature of face stimuli or would be present using non-social stimuli in a similar selective attention task.

Introduction

Outdoor (ambient) air pollution (AAP) is the primary global environmental risk to health that increases mortality worldwide [World Health Organisation (WHO), 2016]. Although adverse effects on cardiovascular and respiratory systems of AAP are well established (Landrigan et al., 2018; Pope and Dockery, 2006), emerging evidence indicates that AAP may also be neurotoxic (Harry and Kraft, 2008; Costa et al., 2017), degrading the brain's cellular structures (de Prado-Bert et al., 2018), leading to neurocognitive decline (Delgado-Saborit et al., 2021) and delaying neurocognitive development (Herting et al., 2019). Specifically, lifetime exposure to AAP has been linked to greater risk of substantial cognitive deficits associated with progressive neurodegenerative diseases such as Alzheimer's Disease (Peters et al., 2019), Parkinson's Disease (Kasdagli et al., 2019), and Multiple Sclerosis (Noorimotlagh, et al., 2020). Chronic AAP exposure is also associated with poorer than expected memory and cognitive executive function in clinically healthy older participants (Gatto et al., 2014). Additional work on the effects of chronic exposure to AAP has focused on children, linking AAP to neuroinflammation (Brockmeyer and D'Angiulli, 2016) and altered neurodevelopment (Calderón-Garcidueñas and Mora-Tiscareño et al., 2008). Cognitive impact of AAP exposure on children has revealed negative effects on psychomotor and sensory processing (Wang et al., 2009), executive cognitive function (Calderón-Garcidueñas et al., 2011; Sunyer et al., 2015; Gui et al., 2020); particularly working memory (Delgado-Saborit et al., 2019; Rivas et al., 2019; Basagaña et al., 2016; Forns et al., 2017) and attention (Sunyer et al., 2017; Rivas et al., 2019).

Although substantial gains have been made in understanding the impact of chronic AAP exposure on cognition in the aging and in the developing brain, few studies have systematically investigated how acute exposure to AAP affects brain function in healthy young adults. Every day, road (HEI Panel on the Health Effects of Traffic-Related Air Pollution, 2010) and rail users (Andersen et al., 2019) are exposed to relatively short bursts of very high levels of AAP (Leavey et al., 2017; Matthaios et al., 2020), yet the acute impact of these events are unknown. Acute exposure to such AAP could cause immediate, mild degradation in brain function if impact on systemic physiological systems was rapid, e.g., interference with gas exchange in the lungs, leading to system-wide de-oxygenation. Alternatively, if acute AAP effects resulted from slower acting inflammatory responses (Calderón-Garcidueñas and Solt et al., 2008; Peters et al., 2006) related to the activation of microglial cells and oxidative stress in the brain (Streit et al., 2004;

Levesque et al., 2011), then functional consequences post-exposure could be delayed by several hours. The aim of the current study was to examine the effects of acute AAP exposure on cognitive function in healthy young adults immediately after AAP exposure and several hours later to distinguish between these two alternative accounts. As the most ubiquitous source of outdoor pollution in urban areas is often traffic-related, this study used a controlled air delivery system to expose participants to diluted diesel exhaust containing a combination of nitrogen oxides (NO_X = $NO + NO_2$) and respirable particulate matter ($PM_{2.5}$) or to clean air (control condition). The diesel exhaust (DE; Schauer et al., 1999) used in the experimental condition is often studied in health-related AAP studies.

Neuroinflammation, without a specific AAP association, has been linked to both psychomotor slowing (Brydon et al., 2008; Balter et al., 2019) and higher-order cognitive consequences, including degradation of attention and social-emotional perception (Allison and Ditor, 2014; Balter et al, 2018; Moieni et al., 2015; Eisenberger et al., 2017; see also Chapters 2 and 3 above). Critically, these consequences are measurable even with very mild inflammation that does not provoke classic signs of sickness behaviour such as fever and social withdrawal (Balter et al. 2019; Balter et al, 2018; Moieni et al., 2015). This raises the possibility that acute exposure to AAP, also not typically associated with sickness behaviour, could nevertheless produce similarly negative effects on cognition. Inhalation of NOx and $PM_{2.5}$, both components of DE, are especially likely to result in neuroinflammatory effects (Oberdörster et al., 2004). Previous studies of acute DE exposure on respiratory health indicate a delayed systemic inflammatory response that peaks between four- and six-hours post-exposure (Nightingale et al., 2000; Salvi et al., 2000), with others showing inflammatory changes between 18- and 20-hours post-exposure (Behndig et al., 2006; Xu et al., 2013), although one study failed to find any change in four widely studied biomarkers of systemic inflammation during this interval (Cliff et al., 2016). These findings support the general prediction that any deficits in cognitive function induced by acute exposure to AAP in the study should be observable after a delay of several hours but not immediately after exposure.

Prior studies of the effects of acute air pollution exposure on cognitive and brain function are sparse and show indeterminate results. Although two electroencephalographic (EEG) studies both reported subtle alterations in brain electrical activity (time-frequency changes) during and up to 2 hours after initial DE or indoor air pollution (cooking) exposure (Crüts et al., 2008; Naseri et

al., 2019), the pattern of activity found was inconsistent between studies and neither study measured changes in behavioural function. Another study of acute exposure to AAP reported immediate, negative cognitive effects on adults (Shehab and Pope, 2019), but the cognitive assessment they used involved tests designed for clinical neurological diagnosis that may be inappropriate for use on non-clinical populations (Gluhm et al, 2013). However, a study of the effects of recent versus chronic natural exposure to AAP on children reported that high recent (within 48 hours) exposure slowed visual information processing speed (Saenen et al., 2016). Similarly, short-term (24 hours) ambient levels of NO_2 and elemental carbon, a DE tracer, were negatively associated with attention function in children (Sunyer et al. 2017). Taken together, these studies provide a mixed picture of the timing and type of effects of acute AAP.

Previous work on the cognitive impact of AAP has lacked precision with regards to cognitive assessment. Like other complex functions, cognition is composed of multiple functional subsystems, each underpinned by a complex connection of multiple brain areas (Posner and Petersen, 1990; Kanwisher, 2010). A core cognitive function, implicated in many different disorders of mental health including schizophrenia, depression, and anxiety, is control over attention (Braff, 1993; Roca et al., 2015; Mathews and MacLeod, 2005). Attention in this context refers to a set of mechanisms that prioritise information processing by selectively boosting neural representations of task-relevant stimuli and suppressing representations of task-irrelevant information (Desimone and Duncan, 1995).

As high-level systems are limited in capacity, the brain uses a proactive control mechanism to plan strategically and enable selective engagement with expected, pertinent information as well as active avoidance of predictable but distracting information. However, a reactive control mechanism is also available for controlling behaviour when sudden, unpredictable events occur. For example, planning to make a coffee requires proactive control to identify and walk towards the kettle, whilst avoiding the biscuit tin, but reactive control might be needed to avoid colliding with a suddenly appearing colleague on the way. These two mechanisms are thought to compete for control over attention with completion of planned tasks dependent on sustained proactive control (Botvinick et al., 1999; Braver, 2012) and distraction by unexpected, task-irrelevant events reflecting reactive control.

Proactive control is typically weakened in mental health disorders that are also associated with neuroinflammation, including depression (Vanderhasselt et al., 2014), anxiety (Schmid et al., 2015), and schizophrenia (Ryman et al., 2018). Moreover, proactive control is negatively affected by obesity, a condition associated with high levels of inflammation (Sellaro, and Colzato, 2017). Easily measured behaviourally, proactive cognitive control is thus a good candidate function to assess in studies of AAP exposure, especially considering its putative sensitivity to acute inflammatory states. Here, cognitive control was measured to assess effects of DE exposure. To enhance the sensitivity of the behavioural test, emotional face stimuli were used as numerous previous studies show that expressive faces are highly compelling distractors, strongly activating reactive mechanisms (Langton et al., 2008) and therefore especially demanding of proactive control mechanisms (Grimshaw et al. 2018).

Method

Within this thesis, Chapter 2 used a proxy of air pollution (candle burning) in an indoor setting and Chapter 3 measured natural-experimental real-life exposure during commuting. To build from this, Chapter 4 returns to a laboratory setting using a TRAP pollution measure of importance within the existing literature (Diesel Exhaust). Critically, the methods used in this Chapter enabled for a better controlled dosing setup and the ability to accurately measure a range of pollutant-species to answer queries remaining from the results of Chapters 2 and 3.

Participants

Sample sizes for this experiment were calculated based on the effect size obtained by ter Huurne et al., (2015) who used an almost identical face recognition to identify differences between RT on one-face and two-face trials between a group administered with an ADHD treatment stimulant (Methylphenidate) and a placebo group. Despite using the same task paradigm, the current study was interested in group differences between two-trial sequences and the influence of diesel exhaust exposure as opposed to singular trial differences. From their results a Cohen's d = 1.6 was calculated for RT difference (one-face trial RT minus two-face trial RT) between drug and placebo groups, i.e., describing a 2-way interaction between stimuli distractibility [one-face (less interference) vs. two-face (more interference)] and medication condition (drug vs. placebo). Recalculating to get Cohen's f (0.5d), this relates to a very large interaction f effect of 0.8. Assuming air pollution exposure would have lower influence on RT than drug ingestion, a medium-large within-between interaction effect size of f = 0.3 and a power of 0.80 were assumed. The result was a required sample size of 96 participants (at least 24 participants in each group) to observe an effect of condition (Diesel Exhaust Immediate; Diesel Exhaust Delay; Clean Air Immediate; and Clean Air Delay) on differences in selective attention as measured by RT on two-trial sequences. G*Power 3.1 (Faul et al., 2007) was used for this analysis.

Ninety staff and student participants aged between 18 and 44 years were recruited through a database held by the University of Manchester and via on and offline advertisements. Individuals who reported current neurological, psychiatric, inflammatory, or respiratory disorders (e.g., multiple sclerosis, depression, rheumatoid arthritis, asthma), use of anti-inflammatory medication during the past 7 days, vaccination within the last 14 days, or current smoking were excluded. Data

from 9 individuals were excluded from all analyses due to their early withdrawal (N = 2), their depression score was +2.5SDs from group mean (N = 3), their sleep quality was +2.5SDs from group mean (N = 1), or their overall behavioural accuracy was less than 70% (N = 3). Table 4.1 shows characteristics of the remaining participants. All procedures were approved by the University of Birmingham Science, Technology, Engineering, and Mathematics Ethical Review Committee (reference number ERN_18-1613). All methods were performed in accordance with relevant guidelines and regulations.

Table 4.1

Demographic Characteristics of Diesel Exhaust Exposure Experiment Sample

Demographic Characteristic	Immediate		Delay	
	Clean Air (CLA-i)	Diesel Exhaust (DE-i)	Clean Air (CLA-d)	Diesel Exhaust (DE-d)
N	19	19	22	21
Mean Age (Years)	23.79 (*7.60*)	22.79 (*7.30*)	22.27 (*3.60*)	21.29 (*3.64*)
Biological Sex (% Female)	74	74	73	76
Body-Mass Index (kg m^{-2})	23.54 (*6.29*)	26.04 (*9.26*)	22.09 (*3.14*)	21.72 (*3.13*)
Depression	5.74 (*5.08*)	5.53 (*5.16*)	4.64 (*5.00*)	3.62 (*4.09*)
Anxiety	3.47 (*5.09*)	4.89 (*5.29*)	4.82 (*3.89*)	3.52 (*3.47*)
Stress	7.95 (*5.49*)	10.05 (*5.94*)	8.73 (*7.02*)	6.48 (*4.66*)
Sleep Quality prior to study	2.84 (*2.19*)	3.05 (*1.13*)	2.77 (*1.27*)	2.71 (*1.06*)
Urbanicity across the lifespan	4.75 (*1.32*)	3.76 (*1.83*)	4.31 (*1.44*)	4.47 (*1.65*)
Number (and percentage) of participants correctly guessing their condition at study end	12 (63.16%)	10 (52.63%)	14 (63.64%)	15 (71.43%)

Note. Numbers in parenthesis indicate standard deviation. One-way ANOVAs were conducted for each demographic. No significant group differences were identified giving us confidence that between-group comparisons are valid and appropriate. Importantly, there was no significant χ^2 association [$\chi^2(3) = 1.520$, $p = 0.678$] between pollution group and self-reported condition accuracy. This implies participants in all pollution groups were equally blind to their condition, validating the double-blind nature of the study

Procedure

Daily, prior to participant arrival, a Volkswagen SD1-1.9 Diesel Engine was run for 20 seconds before injecting air into the atmospheric chamber (DE groups) or outside the building (CLA groups) by a non-experimenter, keeping both the participant and experimenter blind to the daily condition. After informed consent, participants completed a mood questionnaire, height and weight were measured, eucalyptus-scented gel placed under their nose, and they were given a hard candy mint. Participants wore a non-rebreather nose and mouth mask connected to the atmospheric chamber; air was inhaled from the chamber, but exhaled breath expelled into the ventilated testing room. After 60 minutes of air exposure, during which time participants filled out questionnaires, participants then completed a mood and side-effects questionnaire. In the immediate condition, participants subsequently took part in the face identification task (~20 minutes) before being debriefed and paid £25. In the delay condition, participants left the testing area and continued their day as normal, avoiding alcohol and caffeine as per the exclusion criteria. Participants in this group returned 4 hours later to complete the mood and side-effects questionnaire again, take part in the face identification task, were debriefed, and paid £30.

Materials

Face Identification Task

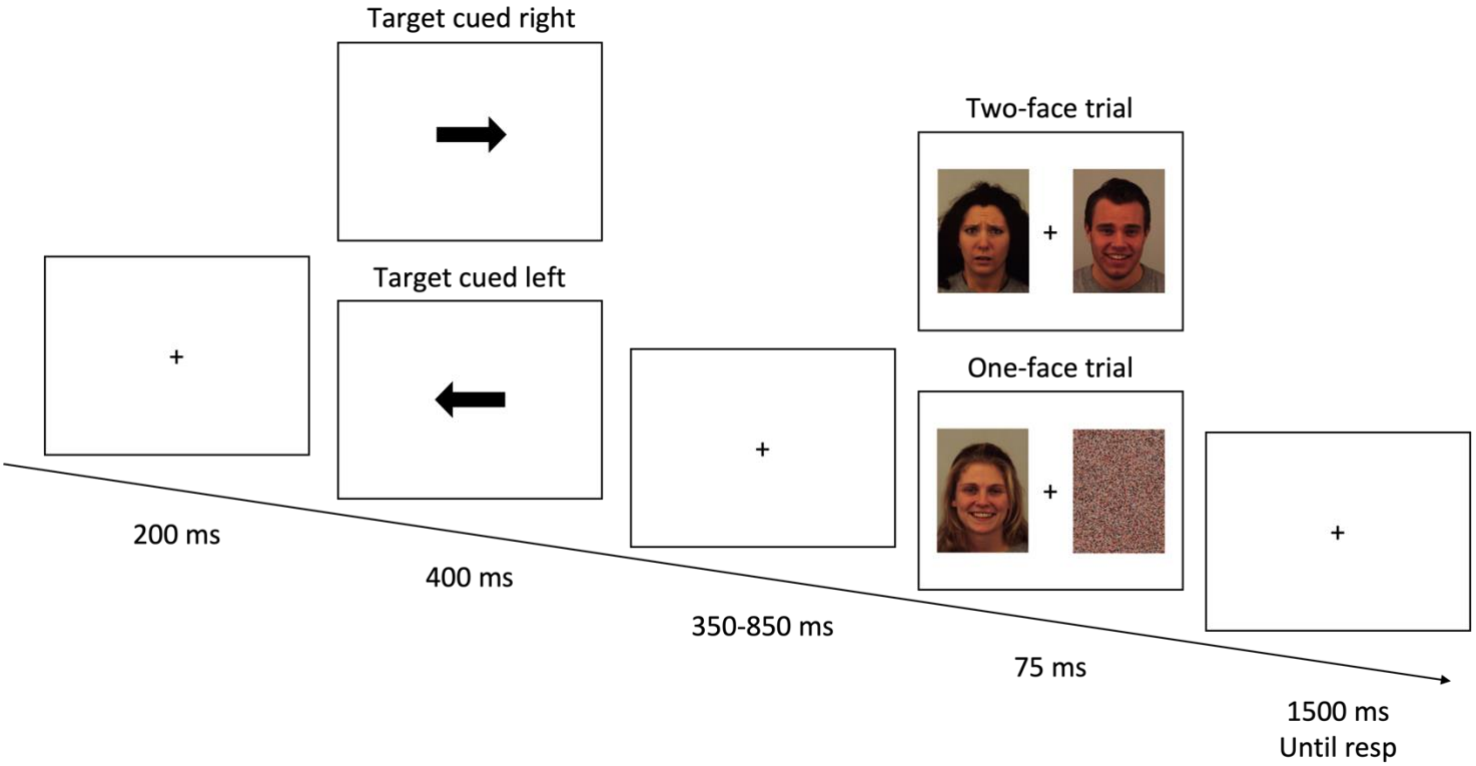
Stimuli. A white spatial cue arrow (2° x 1.5°) pointing left or right and a white centrally presented fixation cross (0.5° in diameter) were used. Faces were gathered from the A set of the Karolinska Directed Emotional Faces (Lundqvist et al., 1998) utilising the frightened (fearful) & smiling (happy) emotional stimuli. Scrambled images were created by splitting face images into 13,984 squares and randomising their position. Each target/distractor image subtended 9° x 12.1°, with the centre of each presented 8.8° of visual angle laterally to the left and right of centre.

Procedure. See Figure 4.1 for the sequence of displays in each trial. Participants were instructed to respond as quickly as possible identifying the target stimulus gender using the ‘a’ or ‘z’ keyboard keys with index and middle fingers of their dominant hand; key assignment to ‘male’ and ‘female’ was counterbalanced between participants. The gender of the target and distraction face was incongruent on 90% of the trials. There were 6 blocks containing 66 trials each, for a total of 396. Second fixation cross was the duration the product of a random integer chosen

between 20 & 50 by frame rate (17 Hz); the target array consisted of one image either side of the fixation cross, for 75 ms; and a final fixation cross presented for 1,500 ms or until participants responded. The target array comprised a central fixation, distractor image (scrambled, happy, fearful), and target image (happy, fearful) with all stimuli combinations equally likely. After the short (75 ms) presentation of the target array, participants were instructed to identify the gender of the target face as quickly and accurately as possible.

Figure 4.1

Illustration of the Face Identification Task



Note. Each trial began with a fixation cross presented for 200 milliseconds (ms), followed by a spatial cue for 400 ms indicating with 100% reliability the location of the upcoming target. After another fixation cross (350 - 850 ms), a target array appeared for 75 ms. The item appearing at the uncued location (distractor) was either a scrambled image or another face. The task was to report the gender of the target face as quickly and accurately as possible.

Atmospheric Chamber

The Manchester Aerosol Chamber (MAC) is a purpose-built chamber comprising an 18m^3 FEP Teflon bag in an air-conditioned enclosure and a high-volume clean air filling system incorporating a series of trace gas and particulate scrubbers. See Shao et al. (2021) for details.

Control of pollutant concentrations was maintained through timed injection of the engine exhaust and the clean air, ensuring similar chemical composition between participants. Cycling between air mix conditions was facilitated by full computer control and monitoring of all necessary chamber conditions. A high-capacity ozone generator served as a cleaning agent during flushing between experiments, occurring daily, with a "harsher" clean carried out weekly.

Participants were fitted with non-rebreather masks attached to the chamber via a plastic pipe, which allowed them to breathe in air from the chamber without forced air pressure. Relative humidity and temperature were measured at several points throughout the chamber and were kept at 50% and 20°C, respectively, to avoid uncomfortable breathing conditions.

Questionnaires

The *Depression Anxiety Stress Scale (DASS) (Lovibond and Lovibond, 1995)* measured recent mental health: Participants rated to what extent 42 statements applied to them over the past week on a scale of 0 to 4 (Did not apply at all - Applied to me very much, or most of the time). The *Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989)* measured participant sleep quality the night prior to testing: This 10-item questionnaire uses objective and subjective questions to determine participant sleep quality over the past month; this was adjusted to refer to the night prior to testing. The *Pollution Exposure Lifestyle Questionnaire (PEL)* was formulated in-house to collect demographic information including postcode and city of previous residence, used to calculate an urbanicity score to ensure no group differences in previous pollution history. A *Mood measure* contained 4 sliding scales from 0 to 100 asking participants to rate their tenseness, irritation, excitement, and happiness. A *Side Effects measure* formed of 9-items asking participants to self-report on a scale of 0 to 4 (No, Mild, Severe, and Extreme) changes in cognition, headache, dizziness, nausea, fatigue, shortness of breath, coughing, throat irritation, and any non-specific uncomfortable feeling, after air exposure.

Data Analyses

Face Identification Task

RTs were excluded from statistical analyses if there was no response, the response was too fast (RT < 150 ms), or the response was incorrect, accounting for 15.3% of data. First trial data

from each block were removed, and individual RTs were trimmed if ±2.5 SDs from mean of 1-face trials, and 2-face trials, accounting for 2.3% of data.

To calculate cognitive control, mean RTs and accuracy scores were subjected to a 2x4 mixed ANOVA using sequence type (change and repeat) as the repeated, and pollution group (CLA-i, DE-i, CLA-d, and DE-d) as the between factor. Socio-emotional processing utilised 2x4 mixed ANOVAs with target emotion (happy, and fearful) as the repeated and pollution group as the between factors for both RT and accuracy on one-face trials. 2x4 mixed ANOVAs were also conducted on two-face trials comparing emotional congruency of stimuli [congruent (target and distractor same emotion), and incongruent (target and distractor different emotion)] as the repeated and pollution group as the between factor. JZS Bayesian statistics were calculated alongside frequentist statistics for these measures.

Conducting analysis using pollution exposure (Clean Air, Diesel Exhaust) and testing time (Immediate, Delay) as two separate factors was considered, however, significant differences in the air mixture, specifically $PM_{2.5}$ concentration, were identified between the DE groups. It was therefore not considered appropriate to include the DE exposures together during the analysis. Instead, analysis used one between-subjects factor with four levels as described previously (CLA-i, DE-i, CLA-d, and DE-d). See Figure 4.3 for more details.

Air Quality

For air quality measures, concentrations for each pollutant were averaged across the one-hour exposure for each participant. 2x2 between-subjects ANOVAs using time of testing (‘immediate’ and ‘delay’) and exposure type (Diesel Exhaust and Clean Air) were conducted for each pollutant.

Levene’s test of Equality of Variances and Mauchly’s Test of Sphericity were used to test for assumption violations; adjustments using the Greenhouse-Geisser correction were made where necessary. Alpha (α) values were set at 0.05 throughout. Bonferroni corrections were applied for multiple comparisons where appropriate. All frequentist analyses were conducted using SPSS v.26.0 (IBM Corp, 2019). All Bayesian analysis were conducted using JASP (JASP Team, 2020).

Summary

Healthy young participants were assigned to one of four groups: Clean Air 'immediate' (CLA-i), Diesel Exhaust 'immediate' (DE-i), Clean Air 'delay' (CLA-d), or Diesel Exhaust 'delay' (DE-d). (See Table 4.1). Prior to air exposure, participants completed a mood measure, rubbed eucalyptus-scented gel under their nose, and were given a hard candy mint to mask any smell or taste of chamber air. During a one-hour air exposure period, participants completed questionnaires providing demographic information; recent sleep quality (PSQI); and depression, anxiety, and stress levels (DASS). CLA groups were exposed to low average concentrations of NO_X [mean = 19 parts per billion (ppb) ± (17)], CO [mean = 281 ppb ± (111)], and $PM_{2.5}$ [mean = 0.08 μg m^{-3} ± (0.08)]; and DE groups exposed to city-street comparable concentrations of NO_X [mean = 524 ppb ± (51)] and CO [mean = 1784 ppb ± (222)], although $PM_{2.5}$ concentrations below WHO limits [mean = 6.97 μg m^{-3} ± (3.22)]. (See Figure 4.3). After exposure, participants then completed a second mood measure and side-effects questionnaire. Those in the immediate groups then completed the cognitive control task illustrated in Figure 4.1. Participants in the delay groups completed another mood and side-effects measure 4 hours later and then the cognitive control task. At the end of their session, participants reported which air type they thought they had breathed.

The cognitive control task required fast, accurate target face gender identification in the presence of another face (2-face trials) or a non-face distractor (1-face trials). Typically, in this task a face distractor slows response time indicating that it has captured reactive selective attention. Numerous studies of cognitive control show that distractor-induced slowing is exacerbated when the preceding trial has no compelling distractor, as in a 1-face trial, compared to when a distractor is present, as in a 2-face trial (Gratton et al., 1992). This is due to prior experience of distractor suppression on trial *n*-1 boosting proactive target processing on trial *n* whereas, when trial *n*-1 does not require suppression, proactive control is weakened leading to increased susceptibility to attention capture by an irrelevant distractor on trial *n* (Egner and Hirsch, 2005). Differences in response time (RT) for 2-face trials preceded by a 2-face trial (repeat sequence) versus RT on 2-face trials preceded by a 1-face trial (change sequence) serves to inversely index proactive cognitive control, i.e., the capacity to maintain strong selection bias for the target, despite recent sensory events. It is therefore expected that RTs would be slower for change versus repeat sequences, and that this effect would be exacerbated after DE exposure due to loss of cognitive control.

Results

Cognitive Control

An analysis of variance (ANOVA) of individual mean RT was used to determine the effect of trial sequence type (repeat, change) and air exposure groups (CLA-i, DE-i, CLA-d, DE-d). As predicted, RTs were significantly slower for change versus repeat sequences [$F(1, 77) = 14.02$, $p < 0.001$, $\eta_p^2 = 0.154$, $1\text{-}\beta = 0.959$]. Critically, this effect depended on air exposure group [$F(3, 77) = 3.33$, $p = 0.024$, $\eta_p^2 = 0.115$, $1\text{-}\beta = 0.737$]. The main effect of air exposure group was non-significant [$F(3, 77) = 0.189$, $p = 0.903$] providing no evidence that acute DE exposure produces generalised psychomotor slowing. (See Table 4.3).

To investigate the interaction of air exposure group and sequence type, RT difference scores (ΔRT = Change minus repeat sequences) were compared across air exposure groups. (See Figure 4.2). For the 'delay' conditions, group mean ΔRT for the DE-exposed group (mean ΔRT = 24, s.d. = 25) was 23 ms larger than that for the CLA-exposed group (mean ΔRT = 1, s.d. = 26), a statistically significant difference [2-tailed, independent sample t-test, $t(41) = -2.89$, $p = 0.012$]. The corresponding difference between the 'immediate' DE-exposed group (mean ΔRT = 8, s.d. = 29) and CLA-exposed group (mean ΔRT = 7, s.d. = 13) was negligible and non-significant [2-tailed, independent sample t-test; $t(36) = -0.042$, $p = 1.934$], Bayesian statistics confirmed the null hypothesis for the comparison between immediate groups ($BF_{excl} = 3.172$).

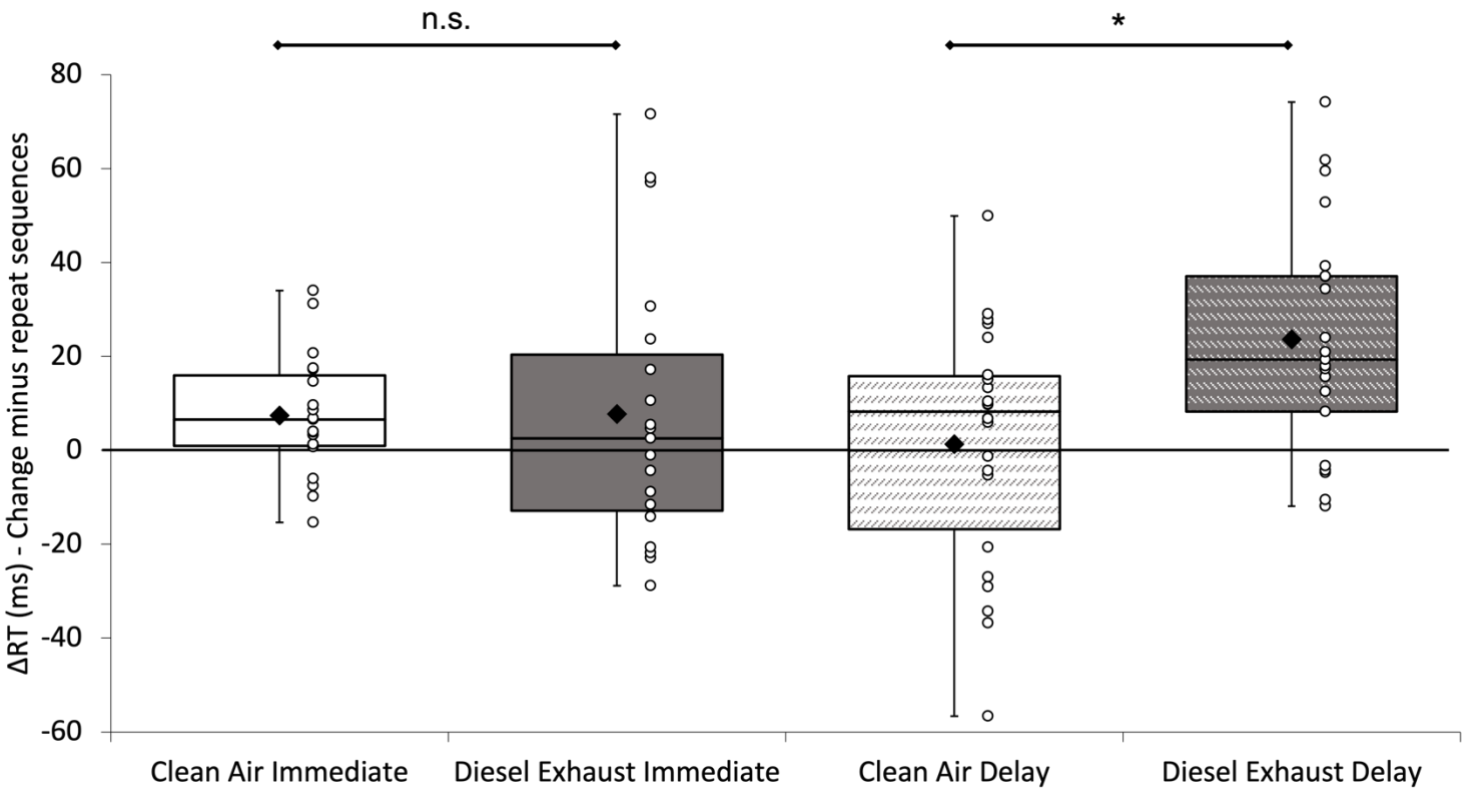
All corresponding analyses of proportion correct responses produced non-significant results. ANOVA of individual proportion correct scores using trial sequence type and air exposure group as between-subjects factors showed only non-significant main and interaction effects ($F < 1$). Acceptance of the null hypothesis regarding proportion correct scores was confirmed using Bayesian analysis ($BF_{excl} > 3$), suggesting RT differences are unlikely to reflect strategic processes such as speed-accuracy trade-offs.

Significant variations in $PM_{2.5}$ concentrations between 'immediate' and 'delay' DE groups led us to investigate whether pollutant concentration for each test time could explain differences in task performance alone. Session average NO, NO_2, NO_X, $PM_{2.5}$ and CO concentrations experienced by individual participants in each testing group ('immediate' and 'delay'), irrespective of exposure group, were correlated with their ΔRT (cognitive control measure). In the 'immediate' conditions no significant correlation was identified between ΔRT and pollutant. Conversely, all

pollutants were significantly positively correlated with ΔRT in the 'delay' conditions, explaining 13-24% of the variance in the data. (See Table 4.2). Together these results argue against the notion that differences in pollutant concentration alone resulted in cognitive control changes, pointing to time of testing as the primary factor to explain the significantly poorer cognitive control identified in the DE-d condition compared to CLA-d.

Figure 4.2

Boxplot showing ΔRT (RT change minus RT repeat sequences) for all Pollution Exposure Groups



Note. Upper and lower boxes show interquartile ranges, with central bar indicating median, and diamond indicating mean; circles indicate individual participants. Higher ΔRTs indicate poorer cognitive control ability. * indicated that ΔRT (change minus repeat sequences) was significantly higher in the Diesel Exhaust delay group [23.66 (*24.62*)] compared to the Clean Air delay group [1.34 (*26.01*)], [$t(41) = -2.89$, $p = 0.012$], corrected for multiple comparisons. No significant group differences were identified in those tested immediately after exposure, indicating that cognitive control ability is poorer four-hours after exposure to diesel exhaust compared to clean air.

Table 4.2

Pearson Correlation Coefficients between ΔRT and Pollutant Concentrations

Pollutant	Cognitive Control (ΔRT)				
	Immediate Testing		Delay Testing		
	r	*p*	*r*	*p*	*Variance (R^2)*
Carbon Monoxide (CO)	0.016	0.922	0.429	0.004 **	18.40%
Nitric Oxide (NO)	-0.030	0.857	0.493	< 0.001 **	24.30%
Nitrogen Dioxide (NO_2)	0.029	0.861	0.362	0.017 *	13.10%
Nitrogen Oxides (NO_X)	0.003	0.986	0.450	0.002 **	20.25%
Particulate Matter ($PM_{2.5}$)	-0.035	0.833	0.361	0.017 *	13.03%

Note. CO, NO, NO_2, and NO_X were log base 10 transformed prior to correlation
* indicates $p < 0.05$ and ** indicates $p < 0.01$

Socio-Emotional Processing

Previous studies of acute inflammation effects on social emotional cognition reported a reduction in the ability to identify emotional expression when viewing the eyes of expressive face photographs (Balter et al., 2018; Moieni et al., 2015). These studies raise the possibility that those in the DE-d condition may have experienced more difficulty interpreting the emotional expression on faces even though emotional information was task irrelevant. To investigate whether this potential processing difficulty could have negatively affected cognitive control, responses on 1-face trials with happy versus fearful face target expressions were compared for each pollution group. RT analysis found neither main nor interaction effects to be significant [Target type: $F(1, 77) = 1.764$, $p = 0.188$, other *F-values* < 1]. A similar analysis of proportion correct scores identified a significant main effect of target type on accuracy [$F(1, 77) = 11.515$, $p = 0.001$, $\eta_p^2 = 0.130$, $1\text{-}\beta = 0.918$], such that accuracy was better for trials with happy [87.9% (*6.3*)] compared to fearful [85.5% (*6.7*)] targets. Critically, the main effect of air-exposure group and its interaction with target type were both non-significant [Interaction: $F(3, 77) = 1.401$, $p = 0.249$; Exposure group: $F < 1$]. Bayesian analysis confirmed the null hypotheses for these effects ($BF_{excl} > 3$). This suggests that differences in perceptual acuity of emotion expression had no significant role in determining two-trial sequence performance.

To further explore a possible influence of face expression on DE effects, individual mean RTs and proportion correct scores in 2-face trials were analysed for face expression congruency effects. Congruent trials, where both faces had the same emotion expression, were compared to incongruent trials, where target and distractor expression differed. For participants sensitive to face expression, the former condition could be considered to have less information than the latter rendering processing easier, an effect that might not benefit those with less facial expression sensitivity. No significant main or interaction effect of expression congruency was identified for RT [Trial congruency: $F(1, 77) = 2.496$, $p = 0.118$; Exposure group: $F < 1$; Interaction: $F(3, 77) = 1.988$, $p = 0.123$]. Bayesian analysis confirmed the null hypothesis for the interaction effect ($BF_{excl} = 3.676$). A similar analysis of proportion correct was also non-significant for both main and interaction effects [Interaction: $F(3, 77) = 1.504$, $p = 0.220$, other *F-values* < 1]. Bayesian analysis further confirmed the null hypothesis for these comparisons ($BF_{excl} > 3$). (See Table 4.3).

Air Quality Measures

There was a significant main effect of air-exposure group identified for all pollutants, with DE concentrations higher than CLA concentrations in all cases ($p < 0.001$). (See Figure 4.3). For $PM_{2.5}$ there was also a significant interaction of time of testing and air exposure [$F(1, 77) = 31.484$, $p < 0.001$, $\eta_p^2 = 0.290$, $1\text{-}\beta = 1$] such that, although concentrations were similar between CLA groups, they were significantly higher for DE-d compared to DE-i (Figure 4.3E). The DE-d group were exposed to almost double (mean = 8.98 $\mu g\ m^{-3}$, s.d. = 2.52) the concentration of the DE-i group (mean = 4.74 $\mu g\ m^{-3}$, s.d. = 2.33) on average. However, average mass concentrations were not higher than the WHO annual limit for $PM_{2.5}$ concentration (10 $\mu g\ m^{-3}$) and all below 24-hour limits (25 $\mu g\ m^{-3}$) for either DE group (Figure 4.3F). No temporal differences in pollutant exposures (interactions) were identified for other pollutants.

Table 4.3

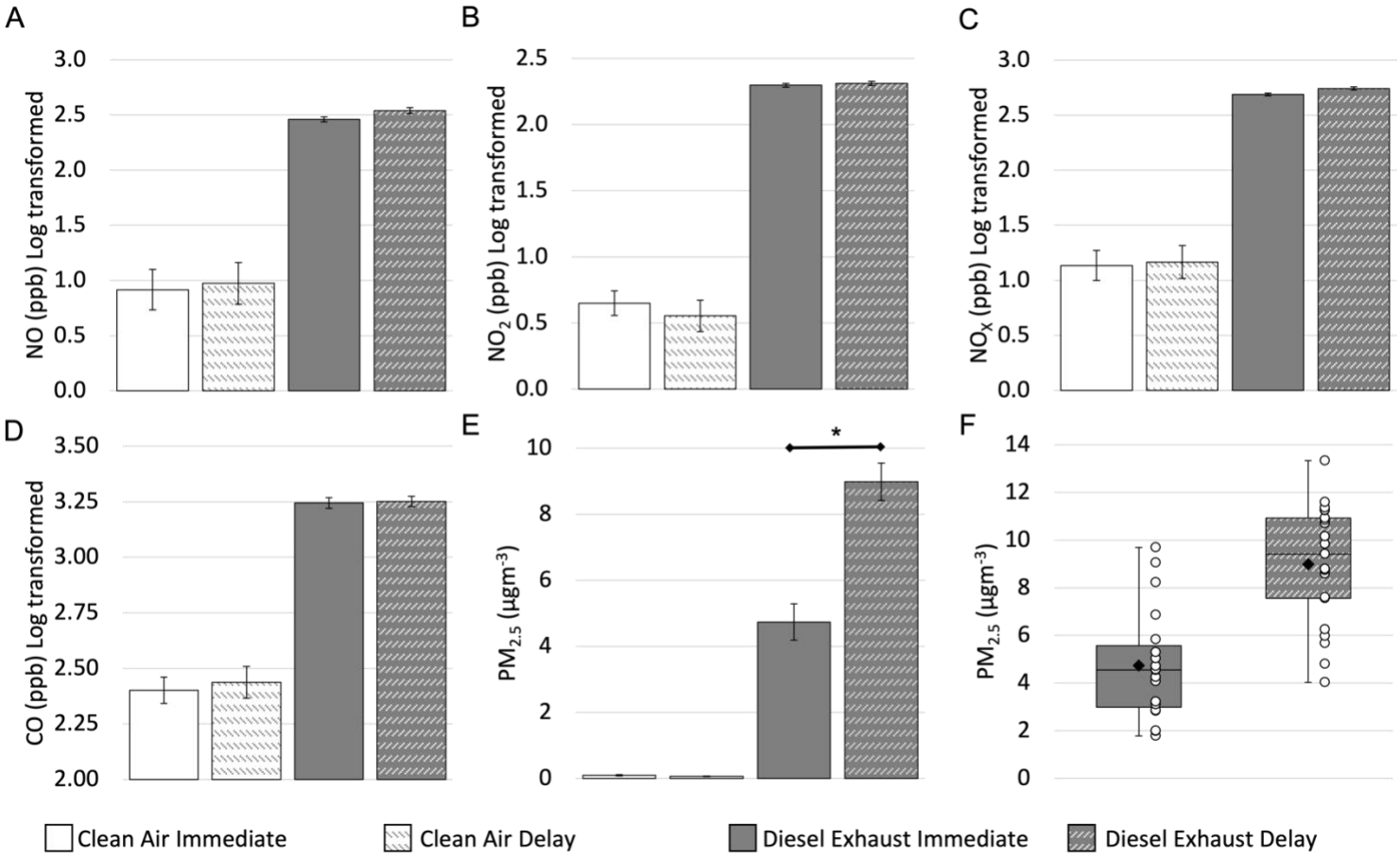
Mean Response Time (RT) and Mean Accuracy (proportion correct) for Target and Distractor Stimuli combinations for all Pollution Exposure Conditions

Trial type		Immediate Testing		Delay Testing		Group		Trial Type		Interaction	
		Clean Air	Diesel Exhaust	Clean Air	Diesel Exhaust	*p*	BF_{excl}	*p*	BF_{excl}	*p*	BF_{excl}
RT (ms)											
One-face trials (Scrambled Distractor)	Happy Target	597 (*99*)	552 (*87*)	574 (*78*)	576 (*96*)	0.605	2.66	0.188	3.96**	0.640	21.51**
	Fearful Target	598 (*99*)	563 (*93*)	574 (*81*)	583 (*105*)						
Two-face trials (Emotional Distractor)	Congruent	619 (*108*)	605 (*112*)	613 (*75*)	619 (*113*)	0.907	2.43	0.118	2.23	0.123	3.68**
	Incongruent	629 (*105*)	599 (*112*)	628 (*79*)	621 (*111*)						
Accuracy (% correct)											
One-face trials (Scrambled Distractor)	Happy Target	89.6 (*5.4*)	89.2 (*4.9*)	85.5 (*6.6*)	87.4 (*7.2*)	0.542	5.89**	0.001*	0.09	0.249	5.20**
	Fearful Target	85.8 (*8.0*)	85.4 (*6.6*)	85.1 (*5.4*)	85.8 (*7.2*)						
Two-face trials (Emotional Distractor)	Congruent	86.1 (*6.7*)	84.0 (*7.9*)	85.3 (*6.2*)	84.9 (*7.0*)	0.808	5.79**	0.827	8.35**	0.220	26.88**
	Incongruent	86.6 (*5.9*)	85.6 (*7.7*)	83.7 (*7.2*)	84.9 (*7.4*)						

Note. Frequentist analysis showed that participants are significantly more accurate when responding to happy compared to fearful emotional targets in 1-face trials. Null hypotheses are confirmed for all interactions
p indicates the statistical significance value of a frequentist 2x4 ANOVA comparing stimuli type and pollution group
BF_{excl} indicates Bayesian factor for null hypothesis testing
* indicates $p < 0.01$ and ** indicates $BF_{excl} > 3$

Figure 4.3

Average Pollutant Concentrations across all Pollution Exposure Groups



Note Graph **A**: shows log base 10 transformed NO concentration (ppb). **B**: log base 10 transformed NO_2 concentration (ppb). **C**, log base 10 transformed NO_X concentration. **D**: log base 10 transformed CO concentration (ppb). **E**: $PM_{2.5}$ concentration (µg m^{-3}) for all groups
Error bars indicating 95% confidence intervals. CLA groups are not significantly different from each other for any pollutant; DE groups are significantly higher than CLA groups for all pollutants. **F**: Boxplot showing $PM_{2.5}$ concentrations in diesel groups with circles indicating individual participant means and diamonds indicating group means
* indicates significant difference between DE groups at $\alpha = 0.05$ level

Eucalyptus-scented gel

The active ingredients in the Eucalyptus-scented gel used to mask the smell of DE were levomenthol, camphor, eucalyptus oil, and turpentine oil. No adverse effects of these ingredients were expected due to the low dose and short (1-hour) time frame. Whilst all participants used the gel regardless of pollution exposure, there is a possibility that turpentine oil may have reacted with the high NO_X concentrations in the DE groups, turning to acid products (Mercier et al., 2009),

potentially increasing toxicity and influencing the study results. In future, another method could be used to blind participants to the exposure, possibly using a nose clip to restrict breathing through the mouth only.

Subjective Measures

To investigate whether effects of loss of cognitive control in the DE-d condition were related to the subjective feelings of sickness behaviour; affect and arousal or to expectation due to awareness of air-exposure condition, self-report measures were compared among air exposure and testing time groups. A χ^2 test indicated no significant association between pollution group and accuracy of participant's identification of their air-exposure condition [$\chi^2(3, N = 81) = 1.520$, $p = 0.678$], supporting the conclusion that awareness of air condition did not account for cognitive control degradation observed in the DE-d group. (See Table 4.1).

All mood measures were unaffected by pollution group and interaction between pollution group and time of assessment (pre-exposure, immediately post-exposure, delayed post-exposure. (See Supplementary Materials Appendix A for details). The absence of subjective changes in mood suggests internal emotional states provide no basis for explanation for cognitive control degradation observed in the DE-d group and suggests participants were unaware of their exposure condition. Supporting the latter point, analyses of side effects subjectively reported immediately after exposure for immediate and delay exposure groups indicated no effect of air-exposure group. This also held for the delay group when side effects were again assessed four hours after exposure. (See Supplementary Materials Appendix B for details). These data indicate that participants did not experience "sickness behaviour" in any conditions, a side effect often reported in vaccination paradigms that itself may alter executive functioning (Keogh et al., 2013).

Discussion

The current study investigated the impact of one-hour diesel exhaust exposure on executive brain function in a healthy adult population. Participants exposed to DE had significantly lower cognitive control compared to those exposed to clean air four hours after exposure, with no differences between groups when tested immediately after exposure. This study provides the first experimental evidence that control over selective visual attention, a critical cognitive function, is impaired in clinically healthy adults hours after a single acute air pollution exposure. Not only does this finding add substantially to the extant research showing a negative correlation between cognitive function and long-term chronic exposure to air pollution, but it also provides evidence that acute air pollution effects are relatively slow acting, consistent with air pollution causing neuroinflammation.

The negative impact of DE exposure identified here is unlikely to be due to "sickness behaviour" as groups did not differ in self-report of physical health or mood alterations after air exposure. Nor are effects easily explained as a psychological demand characteristic resulting from awareness of air exposure condition, as evidence indicates participants were unable to report reliably the condition to which they had been exposed. Although an indirect effect of air pollution on face expression perceptual capacity could potentially account for these findings (as was the main findings in Chapters 2 and 3), an analysis of face expression perception effects on behavioural responses provides no support for this potential confound.

Previous experimental studies on acute effects of air pollution on cognition are sparse. A study using a colour Stroop task that measures task-switching and suppression of automatic responses failed to identify any immediate negative consequences of brief AAP exposure (Shehab and Pope, 2019). Shehab and Pope (2019) used a candle to increase $PM_{2.5}$ concentrations before cognitive testing immediately after exposure, yielding an average concentration of 41.4 $\mu g\ m^{-3} \pm (46.1)$ compared to just 8.98 $\mu g\ m^{-3} \pm (2.5)$ in the current study (DE-d group). Consistent with the current study, no immediate degradation of attention was found. On the other hand, despite the lower average $PM_{2.5}$ concentrations used in the present study, a significant impact of AAP exposure on delayed cognitive control over visual selective attention is reported here. Consistent with the current findings, attention measured using the Stroop task was associated with recent (up to 48 hours) PM exposure in children (Saenen et al., 2016). Likewise, a recent correlational study identified an association in older adults between acute exposure to higher $PM_{2.5}$ concentrations

and lower global cognitive functioning (Gao et al., 2021). On the other hand, Saenen et al., 2016 found no association between recent exposure and attention, using the Continuous Performance test on the same study. The discrepancy in these findings is likely due to the greater sensitivity of selective attention tasks that allow precise response time measures and the ability to examine subtle sequential trial effects that reveal cognitive adaptation to changing events.

The current study was not designed to identify which pollutant in the DE-d condition led to cognitive deficits nor to identify the physiological means by which DE exposure affects brain function. Although the present study utilised relatively low PM concentrations, the concentrations of NO_2 for both DE groups were above WHO guideline limits (WHO, 2005), although not beyond what might be experienced in a busy city street. Thus NO_2, other nitrogen oxides, or CO, could be the cause of the cognitive deficits identified here instead of PM. If so, then hypoxia, whereby the body is deprived of adequate oxygen supply at the tissue level (MacIntyre, 2014), needs to be considered as a potential underlying cause of the cognitive deficits observed here. Acute hypoxia is known to cause memory and executive function performance deficits, e.g., when climbing at altitude (Asmaro et al., 2013) and can eventually cause neuronal cell death (Aw et al., 1987). Milder prolonged (30 minute) exposure to hypoxic conditions can slow response time in selective attention tasks, but these effects peak immediately after exposure and improve significantly within 2 hours, returning to baseline with 24 hours (Phillips et al., 2015). This implies that, if hypoxia were the basis of the cognitive deficits observed here, performance should have been lower for the DE-i compared to the DE-d group, whereas the reverse was observed.

The $PM_{2.5}$ concentrations dropped off over the testing day because of deposition in the chamber, leading to significantly higher concentrations for the DE-d versus DE-i group (as DE-d participants breathed the chamber air earlier in the day). However, ambient $PM_{2.5}$ concentrations from the Manchester Piccadilly fixed site monitor (1.63 km from testing location; https://uk-air.defra.gov.uk/networks/site-info?site_id=MAN3) were on average 10.79 $\mu g\, m^{-3}$ ± 14.37 (the large standard deviation being driven by highly polluting activities overnight between 5th and 6th November 2019 where $PM_{2.5}$ concentrations peak at 175.9 $\mu g\, m^{-3}$) across the testing days. Therefore, participant $PM_{2.5}$ exposure levels during the study in both diesel conditions were similar to or below average ambient levels, indicating that $PM_{2.5}$ may not be the pollutant driving the identified cognitive control effect. In contrast, ambient levels of NO_X (35 ppm ± 24) were much lower than DE group exposure (524 ppb ± 51). This contrast was repeated for CO (Where

measurements were not recorded after 2006: 2006 annual mean CO 262 ppb ± 207) with average DE exposure 1784 ppb ± (222). Whilst these values are not beyond what one might experience during a high exposure event, the exposure concentrations of NO_X and CO were far higher than ambient levels during the study campaign, whereas $PM_{2.5}$ concentrations were comparable. This could suggest that the identified effect of DE on cognitive control were due to the gases in the pollution mixture as opposed to particulates. It is, however, worth noting that WHO $PM_{2.5}$ concentration limits are set lower than the exposure values in this study (5 $\mu g\, m^{-3}$), perhaps indicating that concentrations above these levels may still have adverse health effects. In future, using a repeated-measures design with individual pollutant-species exposures could allow the dissociation between separate pollutants and their effect on cognitive control mechanisms. Reusing the MAC facility would allow for such experiments.

Whilst an immediate acute loss of cognitive control in the DE-d group cannot be ruled out, from the available evidence a delayed response is more likely given the overall low $PM_{2.5}$ concentrations and the necessary time for physiological processes, such as inflammation, to progress. In either case, the cognitive effects of repeated exposure to DE at these levels is of concern.

A candidate process to explain the delayed effect is an inflammatory response that results in modulated neurotransmission. Short-term air pollution exposure has been shown to cause an inflammatory response (Behndig et al., 2006; Xu et al., 2013; Nightingale et al., 2000; Salvi et al., 2000), and vaccination paradigms show that neuroinflammation negatively impacts attentional processing and therefore, potentially, cognitive control, about 6 hours after vaccination (Balter et al. 2019; Allison and Ditor, 2014). These findings are consistent with the speculation that inflammatory responses to AAP led to the observed cognitive deficits in the DE-d group.

A recent study identified an association between acute exposure to higher $PM_{2.5}$ concentrations and lower global cognitive functioning (Gao et al., 2021). Importantly, participants in that study taking anti-inflammatory medications showed less decline of cognitive functioning compared to their counterparts, implying a protective effect of anti-inflammatory medications against worsening cognitive performance due to air pollution exposure. However, the Gao et al., (2021) study did not experimentally manipulate anti-inflammatory dosage, and executive functioning alone was not changed as a result of AAP exposure. Despite these caveats, their results

are consistent with the notion that inflammation is a mechanism whereby AAP exposure may cause cognitive deficit.

In summary, this study reveals for the first time that there is a time-delayed disruption of cognitive control after short-term exposure to diesel exhaust. The implications of this result are significant as humans are frequently exposed to high concentrations of air pollutants in their environment (HEI Panel on the Health Effects of Traffic-Related Air Pollution, 2010; Andersen et al., 2019). Urban citizens including children will typically experience morning and evening peaks in acute exposure, associated with daily commutes. Given the cognitive demands of the commute on drivers and pedestrians, it is reassuring that the results do not find immediate loss of cognitive control after exposure, although an immediate effect at higher PM exposures cannot be ruled-out. Instead, the current study finds delayed loss of control, suggesting that cognitive 'dips' might be experienced in the early afternoon and again in the evening. Although the consequences of such 'dips' is unknown, even subtle degradation of cognitive control likely impacts the quality and ease of decision making (Diamond, 2013) and places strain on emotion control, potentially degrading mental health. It is expected that, all other things being equal, avoiding daily acute exposure (e.g., by shifting work patterns to work from home more often) will be beneficial for cognitive health. Understanding how physical environments impact psychological processes such as cognition is an important component of the emerging picture of how the urban environments, in which most humans now live, affects the health of the species.

The identified reduction in cognitive control 4 hours following DE exposure adds to the evidence presented in Chapters 2 and 3 indicating a delayed reduction in Approach bias 24 hours following PM & TRAP exposure. Whilst the timing of the delayed effect differs, together these experiments provide strong evidence that the effects of air pollution exposure on executive function are not observable immediately following a pollution episode but instead require a time delay for cognitive effects to be observable. The results from the Face Identification Task also provides an indication that executive function alone is impacted by air pollution exposure. Whilst irrelevant to task goals, the Face Identification Task used face stimuli, which may have confounded the identified effects. Use of social vs. non-social stimuli to measure executive functioning using selective attention tasks is investigated in Chapter 5.

Episodic Memory Recall following Diesel Exhaust Exposure*

Introduction

There is evidence that acute air pollution exposure impedes memory processes (Sunyer et al., 2015), with a larger body of literature identifying a negative effect of chronic exposure on working memory (Delgado-Saborit et al., 2019; Rivas et al., 2019; Basagaña et al., 2016; Forns et al., 2017). Indeed, within this thesis there was shown to be an immediate effect of TRAP exposure on episodic memory encoding, where participants exposed to higher concentrations during their commute took more practice, measured in training runs, to encode the location and order of 20 objects compared to those exposed to lower TRAP concentrations; see Chapter 3. However, this identified effect was absent after only PM exposure from candle burning; see Chapter 2. There were no identified effects of air pollution exposure on recall performance, although this was likely due to the training phase of the task procedure ensuring that all participants were performing at the same level prior to the test phase.

As encoding difficulties were identified following exposure to TRAP but not PM, it was suggested that difficulties in encoding ability were due to the specific to pollutant-species present in TRAP rather than particulates. This assumption is also probable given that the immediate nature of the identified effect was likely due to ROS causing a hypoxic effect, rather than inflammation as suggested as the mechanism for all other identified effects within this thesis. As DE also contains key ROS, such as carbon monoxide, finding a similar immediate effect of DE exposure on encoding ability would provide further evidence for hypoxic mechanisms to explain the effect previously described in Chapter 3. Due to potential confounding factors in the procedure of the Memory Arena (Petzka et al., 2021) used in Chapters 2 and 3 (See Chapter 3 discussion), simplifications were made to the task for this study. This changed version of the task is denoted as ‘Memory Task’, which was altered in the following ways:

Firstly, the training phase was removed and replaced instead with a shorter version of the test using different stimuli prior to exposure to give an indication of baseline episodic memory performance. This was done to ensure that no participants were given an advantage of multiple opportunities to encode the sequence and location of objects. The use of a baseline measure was

also critical to ensure memory performance was compared between pre- and post-exposure to show a change in recall as opposed to measuring individual difference.

Secondly, the Arena background was changed from different landscapes to simple colours (red, blue, green, and yellow). This change was to reduce the complexity of visual information on the screen and potentially improve task performance despite the removal of training runs as colour is known to improve episodic memory recall ability (Dzulkifli and Mustafar, 2013).

Thirdly, to remove the influence of participant-initiated encoding strategies, a known individual difference factor impacting recall ability (Kirchhoff, 2009), participants in this version of the task were instructed to use a specific encoding strategy. The encoding strategy was to form a story to associate the shown object with the on-screen location, building on the story with each novel object presented, for example, 'the blue bear used the red bin' whereby the first object (bear) is in the blue section of the arena followed by the next object in the sequence (bin) in the red area. The aim of this strategy was to standardise the mechanism used to encode as changes in strategy use is associated with recall performance (Waris et al., 2021).

Finally, following the significant correlation of temporal and spatial recall performance in Chapter 2 and 3, indicating a difficulty in measuring performance on each facet of the task separately, two separate test phases were used measuring recall for stimuli sequence and spatial location independently.

Based on the results of Chapter 3, it was anticipated that participants in the immediate Diesel Exhaust exposure condition (DE-i) would show greater spatial error and decreased accuracy recalling the sequence between the pre- and post-exposure recall tests compared to the immediate clean air group (CLA-i). No significant differences were expected in the delay exposure groups.

Method

This was part of the main study presented in this Chapter, see Table 4.1 for a reminder of participant and group demographics. There were two versions of the task; the baseline task administered pre-exposure and the object task administered immediately following completion of the Face Identification Task post-exposure.

Stimuli

The circular 'arena' split into four equal segments each a different colour: blue, RGB [80, 65, 255]; yellow, RGB [255, 255, 0]; green, RGB [0, 255, 0]; and red, RGB [255, 65, 65]. The baseline task selected 10 letters at random from the 26 English alphabet letters presented in black arial font surrounded by a white square. (See Figure 4.4). The object task utilised the same images as described in Chapter 2. (See Figure 2.4). However, 18 images were selected from the 50 total instead of 20 in the previous version of the task.

Procedure

Learning

Participants were first shown a circular 'arena' split into four equal sections containing four different colours (blue, green, red, and yellow). As before an image appeared in a pseudo-random location within this arena. 10 seconds later, the next object image appeared with the previous image remaining on the arena. This process was repeated for a total of 18 object images (10 letters of the alphabet for practice version), with separate locations within the arena. Participants were also tasked with remembering the sequential order the objects appeared. Participants were instructed to formulate a narrative to aid in the encoding of the sequence and location as described above.

Spatial test

Following a 5-minute break where participants completed simple mathematical equations (to prevent rehearsal of the story), participants were presented with a random placement of the 18 objects around the arena edge and were required to place them in the correct location on the circular arena. Participants were informed that the order of object placement was not important, and they

could move objects multiple times before submitting their responses (or until 5 minutes had elapsed). (See Figure 4.4A).

Sequential test

Immediately following the spatial test, all objects appeared around the circle edge in the same order as seen in the spatial test. This time, a line appeared below the arena and participants moved objects onto the line from the first object (leftmost) to last object (rightmost). (See Figure 4.4B). Again, participants could make changes throughout and had a maximum of 5 minutes to complete this.

Data Analysis

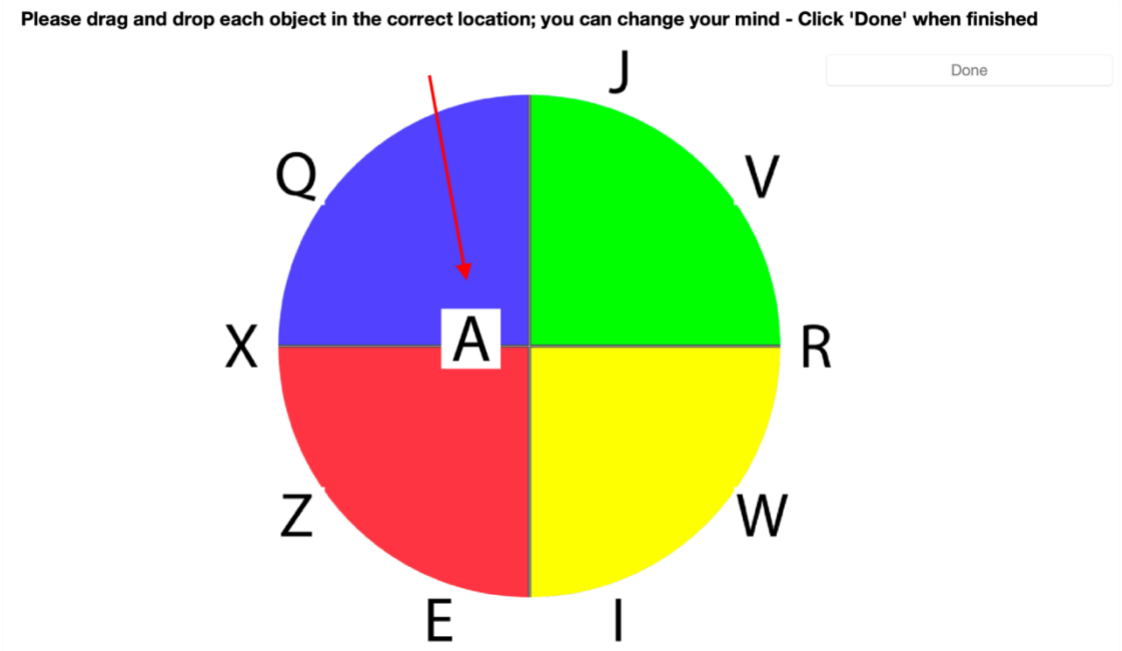
Spatial placement error was calculated once for each chosen object as the straight-line distance in pixels between the centre of the dropped location of the chosen object and the centre of the correct location of that object. Sequential accuracy was scored as correct if the chosen image had been presented just after the previously chosen image regardless of whether the latter had been correctly placed on the line, i.e., if object 6 is next on the line after object 5 this is marked as correct whether object 5 was in position '5' on the line or not.

Two 2x2x2 mixed ANOVAs with between-participants factor pollution exposure group (Clean Air, Diesel Exhaust) and exposure timeline (immediate, delayed) and within-participants factor task-time (pre-exposure, post-exposure) were conducted on spatial error and sequential accuracy respectively. Two between-participants factors were used here instead of the four groups described earlier as time was both a between and within participants factor, critical to understanding the findings despite the identified differences in $PM_{2.5}$ concentration between the DE groups.

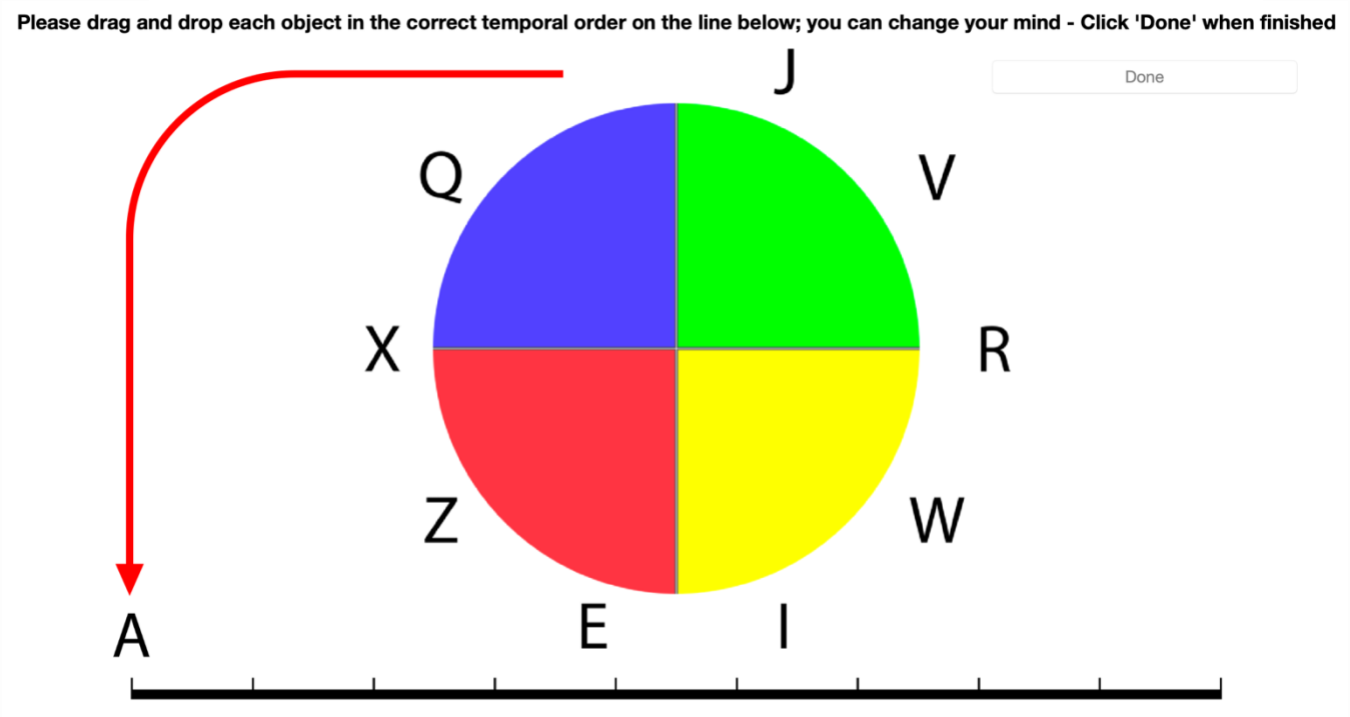
Figure 4.4

Illustration of the **A**: *Spatial and* **B**: *Sequential Test on the Memory Task*

A



B



Note. Red arrow indicates participant dragging of stimuli. Illustration shows the baseline (pre-exposure) task with 10 alphabet letters

Results

Spatial location error

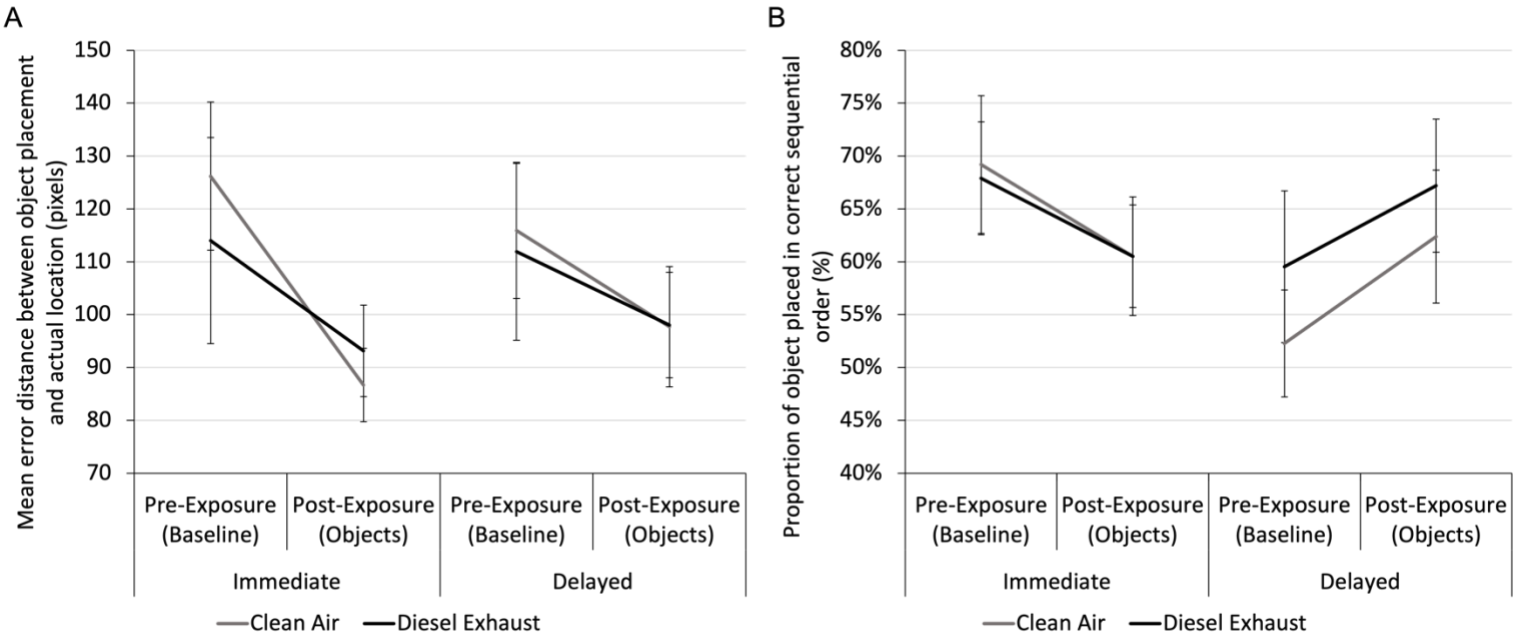
A 2x2x2 Mixed ANOVA (between-participants factors: pollution exposure group and exposure timeline; within-participants factor: task-time) was conducted to identify differences in spatial location placement error between pollution exposure groups, timeline of exposure, and task time. The ANOVA revealed a significant main effect of task time [$F(1, 77) = 404.055$, $p < 0.001$, $\eta_p^2 = 0.840$, $1\text{-}\beta = 1$], such that average spatial error distance (pixels) was higher on the pre-exposure baseline task (mean = 117 pixels, s.d. = 70) compared to the post-exposure task (mean = 94 pixels, s.d. = 43). This was expected as the baseline task gave participants a practice of the task. There were also less stimuli populating the arena so the removal of 'clusters' of stimuli may have played a role too. There were no other significant main effects or interactions identified (All *F-values* < 1), highlighting that pollution exposure group or exposure timeline did not mediate recall of spatial information between the pre- and post-exposure memory tasks. (See Figure 4.5A).

Sequential accuracy

The analysis of variance was repeated for accuracy of sequential placement of images on the line. A significant interaction between task time and exposure time was identified [$F(1, 77) = 6.980$, $p = 0.010$, $\eta_p^2 = 0.083$, $1\text{-}\beta = 0.742$], such that average sequence accuracy in the immediate conditions declined between the baseline (mean = 68.55%, s.d. = 25.60) and post-exposure task (mean = 60.53%, s.d. = 22.52); whereas for the delayed conditions, sequential accuracy increased between the pre-exposure baseline task (mean = 55.81%, s.d. = 28.47) and post-exposure task (mean = 64.70%, s.d. = 28.93). This may be due to higher interference during the post-exposure task for participants in the immediate group due to the shorter time in between the baseline and post-exposure task in comparison to the delayed conditions. The differing stimuli between the pre- and post-exposure task was intended to remove this as a possible confounding variable. Another explanation of this effect may be participant fatigue, whereby participants in the delay condition benefited from a break between task administrations, although this is counterintuitive when considering the delayed effect of DE exposure on cognitive control. There were no other significant main effects or interactions (All *F-values* < 1). This indicated that pollution exposure group did not impact ability to recall the sequence of presented images. (See Figure 4.5B).

Figure 4.5

Line Graphs showing **A**: *Mean Spatial Error Distance and* **B**: *Sequential Accuracy*



Note. Pre-exposure task used 10 alphabet letters and post-exposure task used 18 object images. Error bars indicate standard error. **A**: Mean spatial error calculated as straight-line distance between object placement and actual location (pixels) **B**: Sequential accuracy calculated as proportion of objects placed in correct sequential order (%). No significant main effects or interactions between pollution exposure group and spatial error or sequential accuracy indicating that pollution exposure did not mediate episodic memory performance

Discussion

The results of this study corroborate findings from Chapter 2 and 3; acute exposure to air pollution does not cause dysfunction in temporospatial episodic memory recall. These results somewhat contradict the significantly larger number of training runs required to learn the sequence and location of each objects following high pollution exposure during commuting in Chapter 3. However, the version of the task used in the current study differed significantly from that used in Chapters 2 and 3. By providing an encoding strategy, and removing any training feedback, this metric is not directly comparable to that of the Memory Arena training phase.

This result was somewhat surprising given the identified effect of DE exposure on cognitive control ability in the delay condition, as there is evidence that brain areas involved in cognitive control may also aid episodic memory recall (Wagner, 2002).

Interestingly, participants in the immediate exposure groups performed worse in memory for sequences in the post-exposure task compared to pre-exposure, with the opposite true for the delayed groups which showed an improvement between baseline and post-exposure tasks. Whilst this interaction effect was not mediated by air pollution exposure, it may provide useful information regarding the suitability of this test, the implication here being that those in the immediate exposure conditions were hindered in the post-exposure task due to interference from the more-recently recalled baseline test compared to the delay group, which had 5 hours between the pre-exposure memory task and the post-exposure task.

One potential issue of this task paradigm was that despite providing an encoding strategy for participants, participants may have chosen their own strategy without the knowledge of the experimenter. In future, participants should be explicitly asked which strategy they used to perform the task following study completion to ensure this did not mediate performance (See Waris et al., 2021).

Chapter 5 – Chronic Exposure to High Pollutant Concentrations predicts poor Proactive Control

Abstract

Previous research investigating chronic exposure to air pollution and cognitive function focuses on neurodevelopment (child participants) and neurodegeneration (older participants). Previous literature indicates a correlation between higher air pollution exposure across the lifetime and poorer attention and executive function ability, but effects on clinically healthy young adults remain relatively understudied. In this chapter, lifetime exposure to air pollution was calculated using participant previous residential addresses and compared to performance on sustained attention tasks measuring proactive cognitive control. Learning from prior work on the acute impact of diesel exhaust on cognitive control (See Chapter 4), Experiment 1 used the Face Identification Task to measure proactive control. Data from 51 participants (M_{age} = 18.98, SD_{age} = 0.68) indicated a significant negative relationship between lifetime exposure to air pollution and cognitive control, such that exposure to higher concentrations of pollutants throughout the lifetime predicted lower cognitive control ability as evidenced by larger ΔRTs (R^2 = 0.119). This result mirrored that of the DE study (Chapter 4), however using a chronic exposure paradigm, indicating a reduction in cognitive control after both acute and chronic exposure to high TRAP concentrations. Experiment 2 used the same methodology as Experiment 1 with a Flanker Task measuring conflict adaptation (higher conflict adaptation scores are indicative of lower proactive control). Critically, the Flanker Task used non-social stimuli to identify if the previously identified effect in Experiment 1 was replicated without the use of particularly distracting (therefore engaging of reactive control mechanisms) face stimuli. Data from 164 participants (M_{age} = 18.89, SD_{age} = 0.75) indicated a significant positive relationship between lifetime exposure to air pollution and conflict adaptation, such that exposure to higher concentrations of pollutants throughout the lifetime predicted higher conflict adaptation, indicative of lower proactive control (R^2 = 0.035). This result provided confidence that the previously identified effects of AP on proactive control were not only due to the use of face stimuli. It remains unknown the exact mechanism for the identified effect of lifetime AP exposure on proactive control, and the relationship between cognitive function following acute vs. chronic exposure events. These findings may explain the relationship between high AP exposure and mental health disorders and have implications for decision making and tendencies of risky behaviour in young adults.

Experiment 1 – Chronic Air Pollution Exposure and Cognitive Control

As identified in Chapter 1, high pollution exposure across the lifetime has been linked to cognitive deficits in both neurodevelopment (Calderón-Garcidueñas and Mora-Tiscareño et al., 2008) and ageing (Gatto et al., 2014), with the latter related to the onset of neurodegenerative disease (Delgado-Saborit et al., 2021). This study aimed to expand on the current literature by assessing lifelong air pollution exposure and cognitive control ability in clinically healthy young adult populations.

Evidence links chronic high AP exposure to neuroinflammation (Brockmeyer and D'Angiulli, 2016) and altered neurodevelopment (Calderón-Garcidueñas and Mora-Tiscareño et al., 2008). Studies conducted with children highlight that executive function (Calderón-Garcidueñas et al., 2011; Gui et al., 2020; Harris et al., 2016), and attention (Sunyer et al., 2017) are negatively impacted following chronic exposure to high air pollution concentrations. It stands to reason that exposure to high pollutant concentrations during childhood may have lasting impacts on cognitive function in adult populations, dependent on areas of the brain affected by potential changes to neurodevelopment.

Results from the study in Chapter 4 suggest that cognitive control is reduced 4 hours following acute exposure to DE compared to clean air. Importantly urbanicity score (as a proxy for chronic air pollution exposure) did not differ between groups, providing some indication that previous pollution exposure did not impact this acute effect. However, with evidence that chronic exposure to high pollutant concentrations is related to poorer executive and attentional functioning, it is reasonable that chronic air pollution exposure may elicit a similar negative impact on cognitive control, even if acute high-exposure events may supersede this chronic effect.

Urbanicity score, described in Chapter 2, was calculated using either land-use data (UK only) or the number of inhabitants of an area (International). Considering the spatial variations in air pollution concentration between cities of similar population (Wang et al., 2014), this measure may not be the most valid measure of air pollution concentration. Similarly, those living in the suburbs and centre of a major city would receive the same urbanicity score despite large variations in land-use, and therefore air pollution concentration and composition. Indeed, urban average AP has been shown to scale well with population across Great Britain, but differences from expected concentrations for population size can be significant (MacKenzie et al., 2019). To improve the validity of the urbanicity measure, a separate technique using residential postcode information was

used. The UK-Air UK Ambient Air Quality map (https://uk-air.defra.gov.uk/data/gis-mapping/) provides annual concentrations of multiple pollutants from 2001 through to 2019 (at the time of writing). As the data is split into $1km^2$ squares for each year backdated to 2001, and the average participant age is 19, this tool allowed for high spatial specificity of participant exposures using residential postcodes from birth through to present day.

By utilising residential postcodes to calculate lifetime air pollution exposure, this study aims to investigate the impact of chronic air pollution exposure during neurodevelopment on cognitive control ability using the Face Identification Task from Chapter 4.

It is hypothesised that those exposed to higher pollution concentrations across the lifetime will display less executive control (higher cognitive control score, indexed by ΔRT) compared to those exposed to lower chronic air pollution. It is also hypothesised that lifetime air pollution exposure score will predict this reduction in cognitive control ability.

Method

Participants

As in Chapter 4, sample sizes for this experiment were calculated based on the effect size obtained by ter Huurne et al., (2015) who used an almost identical face recognition to identify differences between RT on one-face and two-face trials between a group administered with an Attention Deficit Hyperactivity Disorder (ADHD) treatment stimulant (Methylphenidate) and a placebo group. Despite using the same task paradigm, the current study was interested in group differences between two-trial sequences and the influence of air pollution exposure as opposed to singular trial differences. From their results a Cohen's d = 1.6 was calculated for RT difference (one-face trial RT minus two-face trial RT) between drug and placebo groups, i.e., describing a 2-way interaction between stimuli distractibility [one-face (less interference) vs. two-face (more interference)] and medication condition (drug vs. placebo). Recalculating to get Cohen's f (0.5d), this relates to a very large interaction f effect of 0.8. As in Chapter 4, assuming air pollution exposure would have lower influence on RT than drug ingestion, a medium-large within-between interaction effect size of f = 0.3 and a power of 0.80 were assumed. The result was a required sample size of at least 24 participants in each group to observe an effect of condition (High vs. Low chronic pollution exposure) on differences in selective attention as measured by RT on two-trial sequences. G*Power 3.1 (Faul et al., 2007) was used for this analysis.

Undergraduate students at the University of Birmingham, Birmingham, UK were recruited through an online research portal and offered course credit on completion of the tasks. Individuals who reported current neurological, psychiatric, inflammatory, or respiratory disorders (e.g., multiple sclerosis, depression, rheumatoid arthritis, asthma), cold or flu symptoms in the past 14 days, vaccination within the last 14 days, or current smoking were excluded. Participants must have permanently resided in the United Kingdom from birth to present day to calculate comparable lifetime pollution exposure scores from one dataset.

Data from 57 students was collected. All data from 6 individuals were excluded from all analyses for the following reasons: missing data (N = 1), depression score was +2.5SDs from overall means (N = 2), anxiety score was +2.5SDs from overall means (N = 1), stress score was +2.5SDs from overall means (N = 1) and accuracy on the task was below 70% (N = 1). Table 5.1 shows the characteristics of the remaining participants.

Table 5.1

Demographic Characteristics of Chronic Pollution Exposure Experiment 1 Sample

Demographic Characteristic	All participants (*n* = 51)	Low Air Pollution (*n* = 25)	High Air Pollution (*n* = 26)	*p-value*	*t-value*
Mean Age (Years)	18.98 (*0.68*)	18.96 (*0.73*)	19.00 (*0.63*)	0.836	-0.209
Sex (% Female)	88.24	92.00	84.62		
BMI (kg m^{-2})	21.65 (*2.20*)	21.79 (*2.32*)	21.51 (*2.12*)	0.649	0.458
Depression	4.76 (*4.62*)	5.08 (*5.09*)	4.46 (*4.20*)	0.637	0.474
Anxiety	4.35 (*3.74*)	4.40 (*3.14*)	4.31 (*4.30*)	0.931	0.087
Stress	9.04 (*6.15*)	9.00 (*6.41*)	9.08 (*6.01*)	0.965	-0.044
Sleep Quality (Overnight)	2.27 (*1.46*)	2.24 (*1.69*)	2.31 (*1.23*)	0.870	-0.164
Autism Spectrum Quotient	14.08 (*5.95*)	14.00 (*5.89*)	14.15 (*6.12*)	0.928	-0.091
Chronic Pollution Score	54.33 (*16.11*)	40.77 (*9.23*)	67.36 (*8.77*)		

Note: Standard deviation in parentheses. T-tests conducted between the Low and High chronic pollution exposure conditions showed no significant differences among demographic characteristics at $\alpha = 0.05$ level.

Design

All procedures were approved by the University of Birmingham Science, Technology, Engineering, and Mathematics Ethical Review Committee (reference number ERN_18-1613). All methods were performed in accordance with relevant guidelines and regulations. This study used a between-participant quasi-experimental design. The naturally occurring between-subjects factor was chronic air pollution exposure. Participants were split into a high or low chronic exposure group based on a median split. The median pollution exposure score was 55.36 (range: 22.57 – 87.24; interquartile range: 42.77 – 65.14).

Materials

All questionnaires and tasks were the same as that of Chapter 4 with the addition of the Autism Spectrum Quotient (ASQ) Questionnaire described below. This was included to ensure that individual differences in emotion recognition ability were not impacting cognitive control effects, due to the expressive stimuli used in the task.

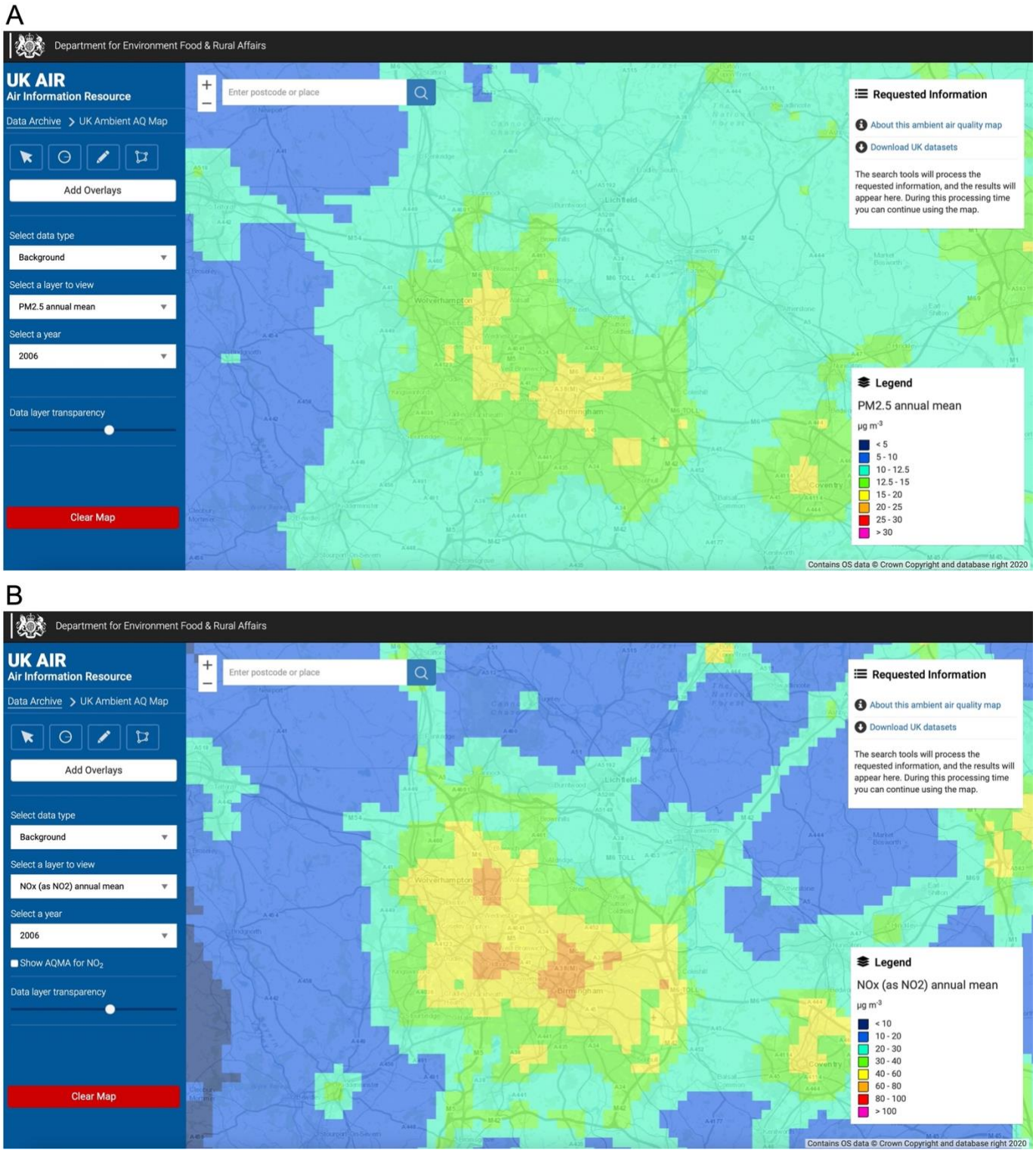
Chronic Pollution Exposure Score

Participant chronic pollution exposure score was calculated using the UK-Air UK Ambient Air Quality Map (https://uk-air.defra.gov.uk/data/gis-mapping/) available from the Department for Environment, Food, and Rural Affairs (DEFRA). This Geographic Information System (GIS) tool provides yearly average modelled data (UK's Pollution Climate Mapping model) of common air pollutants split into $1km^2$ squares across the UK. The tool contains modelled data from 2001 to 2019 for NO_X and PM_{10} with data from 2002 to 2019 for $PM_{2.5}$ all measured in $\mu g\ m^{-3}$. The tool interface, illustrated in Figure 5.1, provides colour-coded ranges of concentration values for each $1km^2$ square. When extracting data, the minimum value of the range was reported i.e. '<5' = 0, '5-10' = 5, '10-12.5' = 10 and so on. Average annual values of NO_X, PM_{10}, and $PM_{2.5}$ were extracted for each year spent at the residential postcode of each participant. When a change in residence occurred during the calendar year, concentration values were averaged across locations, weighted by number of months spent in each location i.e., when starting university, students may have moved from home to live in Birmingham in October. Annual NO_X for that year would be calculated as [((Home NO_X * 9 months) + (Birmingham NO_X * 3 months)) / 12 months]. Yearly concentrations were averaged for each participant, providing an average lifetime pollution exposure value for each pollutant. Then, the individual lifetime average concentrations of each pollutant were summed to create a chronic air pollution score for each participant (Chronic pollution exposure score = Mean Lifetime NO_X + Mean Lifetime PM_{10} + Mean Lifetime $PM_{2.5}$).

This aggregate score was chosen to represent personal chronic pollution exposure for several reasons. The method of calculation provides only an indication of lifetime exposure to air pollution; without data regarding school and indoor air pollution exposures, it is not feasible to calculate true personal-level lifetime exposure. Summing all concentration scores provided the largest variance of considered methods, allowing for an effective median split of the data. Pollutants were not considered separately as there was no prior hypothesis formed to suspect a greater influence of chronic exposure to any specific pollutant-species on cognitive performance based on mixed results in previous studies (Gatto et al., 2014; Tonne et al., 2014; Ailshire and Crimmins, 2014; Wang et al., 2009; Sunyer et al., 2015). There is an indication that NO_X concentration had a slightly higher contribution than particulates to the calculated score, however considering the strong correlations between pollutant-species concentrations (see Table 5.3), the aggregate score was considered fit for purpose as a predictor of lifetime AP exposure.

Figure 5.1

DEFRA Ambient Air Quality Map for **A**: *$PM_{2.5}$ and* **B**: *NO_X*



Note: Example shows modelled annual mean concentrations for an area in the West Midlands, England, in 2006

Autism Spectrum Quotient (ASQ)

With evidence suggesting that brain areas related to social stimuli processing are less active in those with Autism (Pelphrey and Carter, 2008), the Autism Spectrum Quotient was included in this study to ensure no confounding effect of emotion perception on task performance. This self-report questionnaire is formed of 50 statements and designed to measure Autism-Spectrum traits (Baron-Cohen et al., 2001b). Participants rate how strongly they agree or disagree with each statement; definitely agree, slightly agree, slightly disagree, or definitely disagree. Possible scores range between 0 and 50 with a score 26 or above indicating that an individual may be clinically autistic.

Face Identification Task

This task was the same as that used for Chapter 4, described again here in full for clarity.

Stimuli. A white spatial cue arrow (2° x 1.5°) pointing left or right and a white centrally presented fixation cross (0.5° in diameter) were used. Faces were gathered from the A set of the Karolinska Directed Emotional Faces (Lundqvist et al., 1998) utilising the frightened (fearful) & smiling (happy) emotional stimuli. Scrambled images were created by splitting face images into 13,984 squares and randomising their position. Each target/distractor image subtended 9° x 12.1°, with the centre of each presented 8.8° of visual angle laterally to the left and right of centre.

Procedure. See Figure 4.1 for the sequence of displays in each trial. Participants were instructed to respond as quickly as possible identifying the target stimulus gender using the ‘a’ or ‘z’ keyboard keys with index and middle fingers of their dominant hand; key assignment to ‘male’ and ‘female’ was counterbalanced between participants. The gender of the target and distraction face was incongruent on 90% of the trials. There were 6 blocks containing 66 trials each, for a total of 396. Second fixation cross was the duration the product of a random integer chosen between 20 & 50 by frame rate (17 Hz); the target array consisted of one image either side of the fixation cross, for 75 ms; and a final fixation cross presented for 1,500 ms or until participants responded. The target array comprised a central fixation, distractor image (scrambled, happy, fearful), and target image (happy, fearful) with all stimuli combinations equally likely. After the short (75 ms) presentation of the target array, participants were instructed to identify the gender of the target face as quickly and accurately as possible.

General Procedure

Participants first completed the DASS, PSQI, ASQ, and PEL questionnaires. Following this, participants took part in the Face Identification Task (~20 minutes) and were debriefed and provided with course credit upon completion of this.

Data Analyses

Face Identification Task

Response Times (RTs) were excluded from statistical analyses if there was no response, the response was too fast (RT < 150 ms), or the response was incorrect, accounting for 18.25% of the data. First trial data from each block were removed, and individual RTs were trimmed if ±2.5 SDs from mean of 1-face trials, and 2-face trials, accounting for 0.3% of data.

As in Chapter 4, to calculate cognitive control, mean RTs and accuracy scores were subjected to a 2x2 mixed ANOVA using sequence type (change and repeat) as the repeated factor, and pollution group (Low Pollution Exposure and High Pollution Exposure) as the between factor. Socio-emotional processing utilised 2x2 mixed ANOVAs with target emotion (happy and fearful) as the repeated and pollution group as the between factors for both RT and accuracy on one-face trials. 2x2 mixed ANOVAs were also conducted on two-face trials comparing emotional congruency (congruent and incongruent) as the repeated and pollution group as the between factor.

Lastly, a simple linear regression was conducted to identify the relationship between cognitive control and chronic pollution exposure score.

Results

Face Identification Task

Cognitive Control

An analysis of variance (ANOVA) of individual mean RT was used to determine the effect of trial sequence type (repeat, change) and air exposure groups (Low Chronic Exposure, High Chronic Exposure). RTs were significantly longer for change (mean = 546 ms, s.d. = 117) compared to repeat sequences [mean = 536 ms, s.d. = 116; $F(1, 49) = 11.389$, $p = 0.001$, $\eta p^2 = 0.189$, $1\text{-}\beta = 0.911$]. There was no significant main effect of chronic pollution group [$F(1, 49) = 2.388$, $p = 0.129$], but there was an interaction between chronic pollution exposure group and sequence type [$F(1, 49) = 6.763$, $p = 0.012$, $\eta p^2 = 0.121$, $1\text{-}\beta = 0.722$]. Data was collapsed into ΔRT (RT change minus RT repeat sequences) to investigate the interaction effect.

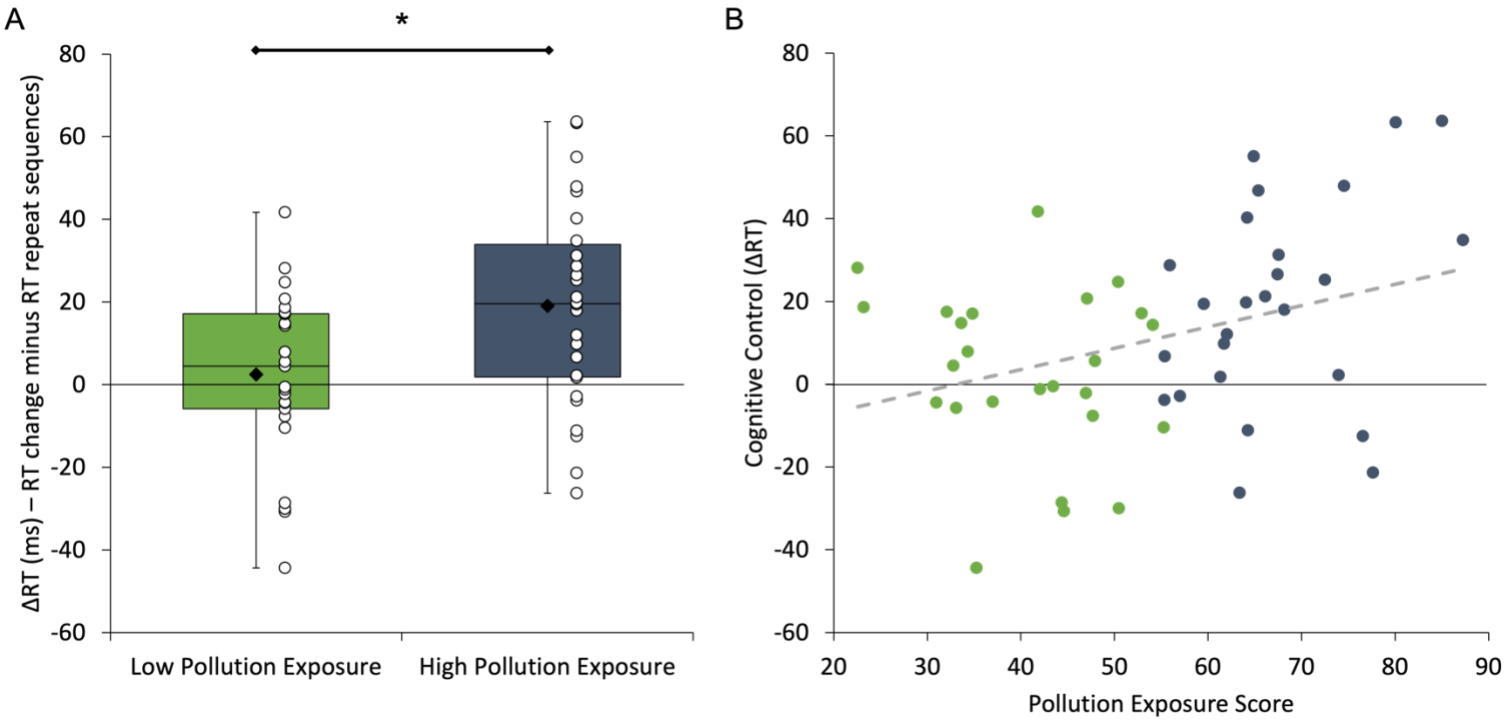
An independent samples T-test identified that ΔRT was significantly higher in the high chronic pollution exposure group (mean ΔRT = 19 ms, s.d. = 25) compared to the low chronic exposure group [mean ΔRT = 3 ms, s.d. = 21; $t(49) = -2.610$, $p = 0.012$]. This result suggests that cognitive control was reduced in the participants exposed to higher pollution exposure across the lifetime. (See Figure 5.2A).

Lastly, a simple linear regression was used to examine the relationship between the predictor, chronic pollution exposure score, and the criterion, cognitive control as indexed by ΔRT. Despite a low amount of variance explained by the model ($R^2 = 0.119$), as hypothesised, pollution exposure throughout the lifetime was a significant predictor of cognitive control, $F(1, 49) = 6.613$, $p = 0.013$. There was a significant positive relationship between pollution exposure score and ΔRT ($T = 2.572$, $p = 0.013$) with ΔRT increasing with increases in chronic pollution score. The model predicts that a 10 unit increase in pollution score would result in a ΔRT increase of 5 ms. (See Figure 5.2B).

ANOVA of individual proportion correct scores using trial sequence type and air exposure group as between-subjects factors showed only non-significant main and interaction effects [pollution exposure group: $F(1, 49) = 2.992$, $p = 0.090$; other *F-values* < 1], providing evidence that the identified cognitive control effects were not due to speed-accuracy trade-off mechanisms.

Figure 5.2

A: *Boxplot showing ΔRT (RT change minus RT repeat sequences) for both Chronic Pollution Groups.* **B**: *Scatterplot comparing Cognitive Control and Pollution Exposure Score*



Note. **A**: Upper and lower boxes show interquartile ranges, with central bar indicating median, and diamond indicating mean; circles indicate individual participants. Higher ΔRTs indicate poorer cognitive control ability. The High chronic pollution group showed significantly lower cognitive control ability (higher ΔRT) than the Low pollution exposure group [$t(49) = -2.610$, $p = 0.012$]. **B**: Green dots indicate those in the Low chronic pollution exposure group and blue circles indicate High exposed participants, split at the median score of 55.36. There was a significant positive relationship between ΔRT and pollution exposure [$F(1, 49) = 6.613$, $p = 0.013$].

Socio-Emotional Processing

To investigate whether a potential processing difficulty in interpreting the emotional expression of faces was present, responses on 1-face trials with happy versus fearful face target expressions were compared for each pollution group. RT analysis found neither main nor interaction effects to be significant [Pollution exposure group: $F(1, 49) = 1.738$, $p = 0.194$, other *F-values* < 1]. A similar analysis of proportion correct scores also identified no significant main or interaction effects of target type on accuracy [Target expression: $F(1, 49) = 1.171$, $p = 0.285$; pollution exposure group: $F(1, 49) = 1.587$, $p = 0.214$; interaction $F < 1$].

To further explore a possible influence of pollution exposure on face expression, individual mean RTs and proportion correct scores in 2-face trials were analysed for face expression congruency effects. Congruent trials, where both faces had the same emotion expression, were compared to incongruent trials, where target and distractor expression differed. For participants sensitive to face expression, the former condition could be considered to have less information than the latter making processing easier, an effect that might not benefit those with less facial expression sensitivity. No significant main or interaction effect of expression congruency were identified for RT [Pollution exposure group: $F(1, 49) = 2.115$, $p = 0.152$; other *F-values* < 1]. A similar analysis of proportion correct was also non-significant for both main and interaction effects [Pollution group: $F(1, 49) = 2.879$, $p = 0.096$; interaction: $F(1, 49) = 1.043$, $p = 0.312$; trial congruency $F < 1$]. (See Table 5.2). These results suggest that chronic air pollution exposure, as measured by the air pollution index, did not influence perceptual acuity of emotion expression.

Table 5.2

Mean Response Time (RT) and Mean Accuracy (proportion correct) for Target and Distractor Stimuli combinations for both Chronic Pollution Exposure Conditions

Trial type		Low Air Pollution (*n* = 25)	High Air Pollution (*n* = 26)	Group		Trial Type		Interaction	
				p-value	*F-value*	*p-value*	*F-value*	*p-value*	*F-value*
RT (ms)									
One-face trials	Happy Target	496 (*99*)	533 (*96*)	0.194	1.738	0.571	0.326	0.981	0.001
	Fearful Target	499 (*103*)	536 (*102*)						
Two-face trials	Congruent	515 (*112*)	564 (*120*)	0.152	2.115	0.631	0.234	0.464	0.546
	Incongruent	516 (*116*)	560 (*111*)						
Accuracy (% correct)									
One-face trials	Happy Target	88.6 (*6.6*)	85.1 (*8.7*)	0.214	1.587	0.285	1.171	0.570	0.454
	Fearful Target	86.8 (*8.7*)	84.8 (*9.9*)						
Two-face trials	Congruent	87.2 (*7.5*)	83.0 (*8.3*)	0.096	2.879	0.465	0.541	0.312	1.043
	Incongruent	87.0 (*7.7*)	84.1 (*8.0*)						

Note. p-value indicates the statistical significance value of frequentist 2x2 ANOVAs comparing stimuli type and pollution group; no significant differences identified.

Air Quality Measures

Chronic Pollution Exposure Score

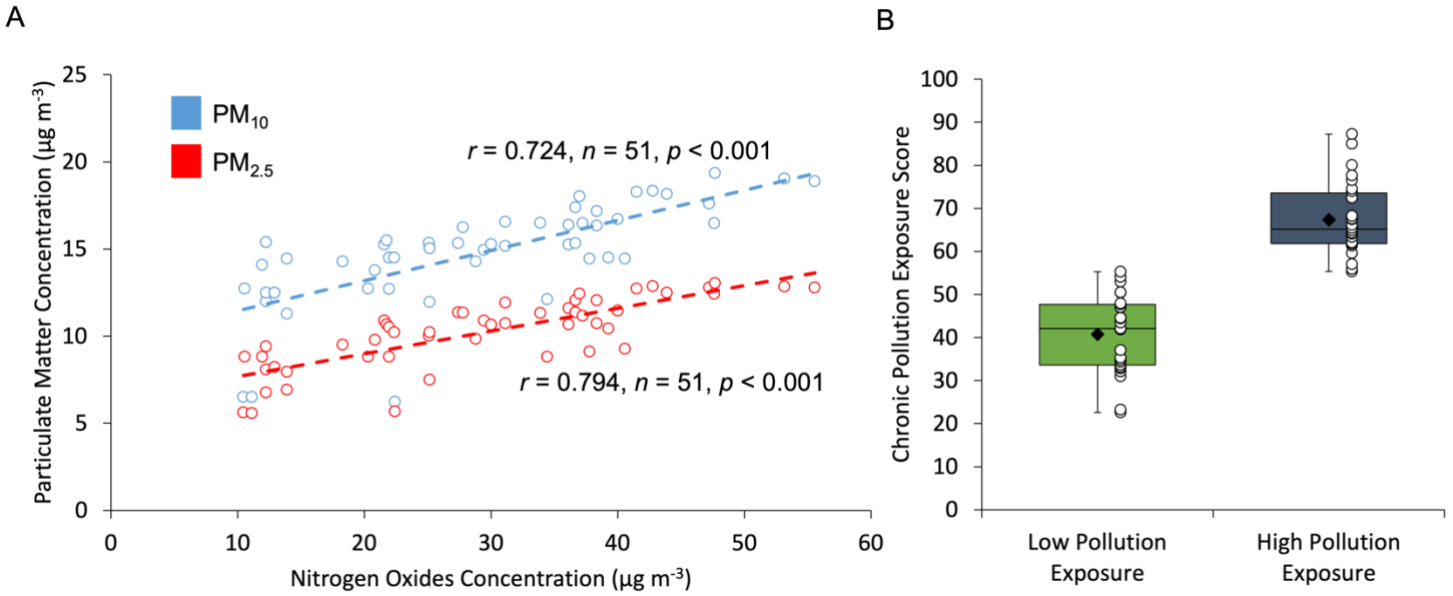
As described in the methodology section, average lifetime NO_X, $PM_{2.5}$, and PM_{10} concentrations were summed to create a pollution exposure score for each participant. To assess the relationship between the modelled pollutant-species, linear correlation analyses were conducted between each pollutant (NO_X, $PM_{2.5}$, and PM_{10}) and chronic pollution score.

The average chronic pollution exposure score was 67 ± (9) in the High exposure group and 41 ± (9) in the Low exposure group. (See Figure 5.3B). Chronic pollution exposure score was highly positively correlated to average lifetime NO_X, $PM_{2.5}$, and PM_{10}. (See Table 5.3). This was expected as the chronic pollution score is a sum of these three values. $PM_{2.5}$ and PM_{10} values were the most highly correlated ($r = 0.934$, $n = 51$, $p < 0.001$), with strong correlations between NO_X and PM_{10}, as well as NO_X and $PM_{2.5}$. (See Figure 5.3A). This indicated that lifetime background concentrations of NO_X, $PM_{2.5}$, and PM_{10} were highly related, making the case for an aggregate score as opposed to separate investigation of each pollutant.

Although acute pollution exposure was not directly measured, all participants travelled to the study from residences in Birmingham. Most participants travelled from postcodes starting B29 or B15, roughly 20 minutes walking time from the testing location. This provided some indication that acute exposure would have been somewhat homogenous across participants.

Figure 5.3

A: *Line Graph comparing NO_X to PM_{10} and $PM_{2.5}$ Concentrations.* **B**: *Boxplot indicating Mean aggregate Chronic Pollution Exposure Score between Pollution Groups*



Note. **A**: Significant strong positive correlations were identified between NO_X and $PM_{2.5}$, and NO_X and PM_{10}. **B**: Circles indicate individual participants and diamonds indicate group mean

Table 5.3

Comparison of Pollutant Concentrations and Chronic Exposure Score in Experiment 1

Pollutant	Low Air Pollution (*n* = 25)	High Air Pollution (*n* = 26)	All Participants (*n* = 51)	*r-value*		
				1	2	3
1. Chronic Pollution Score	40.77 (*9.23*)	67.36 (*8.77*)	54.33 (*16.11*)	—	—	—
2. NO_X (µg m^{-3})	18.95 (*6.23*)	39.30 (*6.79*)	29.33 (*12.13*)	0.981	—	—
3. $PM_{2.5}$ (µg m^{-3})	8.84 (*1.72*)	11.51 (*1.20*)	10.20 (*1.99*)	0.890	0.794	—
4. PM_{10} (µg m^{-3})	12.97 (*2.77*)	16.56 (*1.70*)	14.80 (*2.90*)	0.841	0.724	0.934

Note. Values in parentheses indicate standard deviations. *r-value* indicates the correlation coefficient between pollutants and scores. Significant strong positive correlations were identified between all individual pollutants and pollutant exposure score (*p-values* < 0.001)

Discussion

In this study, participants' chronic pollution exposure was estimated using postcodes of UK residences across the lifetime. These scores were used as a naturally occurring independent variable to form a 'High' and 'Low' chronic pollution exposure group using a median split. Cognitive control ability was measured using the Face Identification Task and was compared between pollution exposure groups. Those in the High pollution group showed higher ΔRT compared to those in the Low pollution group, indicating lower executive function ability. Regression analyses also suggested a negative relationship between chronic pollution score and cognitive control, such that higher chronic pollution exposure scores predicted lower cognitive control ability (higher ΔRTs).

These results may suggest that lifetime exposure to air pollution can predict executive processing dysfunction in clinically healthy adult participants, building on data suggesting the same pattern of result in children (Calderón-Garcidueñas et al., 2011; Gui et al., 2020; Harris et al., 2016). If the neuroinflammation hypothesis explains the reduction in cognitive control following DE exposure seen in Chapter 4, it may be that lifetime exposure to pollutants may cause a constant heightened state of brain inflammation. Indeed, brain-tissue post-mortem analysis of residents in regions of high AP concentrations show higher concentrations of pro-inflammatory markers than in residents of lower AP regions (Block and Calderón-Garcidueñas, 2009). However, Tripathy et al., (2021) suggests that chronic exposure to air pollution may result in more immune reactivity to *acute* exposure episodes as opposed to a general increase in circulating inflammatory agents. This could also explain the current finding assuming all participants were exposed to similar AP concentrations in the 24 hours prior to task administration (Based on evidence presented in Chapters 2, 3, and 4). In this case, high chronic exposure could lead to greater reactivity to acute AP exposure episodes, reducing cognitive control, even if experienced acute concentrations are the same as low-chronic pollution counterparts.

Another explanation of the identified reduction in cognitive control is that repeated exposure to high concentrations of air pollutants during childhood may have stunted neurodevelopment. This explanation is especially compelling considering the prefrontal cortex (PFC), responsible for attention modulation (Miller, 2000), is not fully developed until about 25-years of age (Casey et al., 2008). Indeed, evidence suggests that PFC volume is lower in adults exposed to higher concentrations of air pollution across the lifetime (Gale et al., 2020), with a 5

unit increase of $PM_{2.5}$ concentration ($\mu g\ m^{-3}$) predicting a 1% decrease in PFC volume. This figure parallels with the reduction in PFC volume per year (0.9%) in ageing (Raz et al., 2005). Considering the average age of the experimental sample was 19 years old, it may be the case that chronic AP exposure has impacted the development of this brain area, critical for executive processing.

The PFC is not the only brain area critical for performance on tasks requiring cognitive control. Evidence from functional Magnetic Resonance Imaging (fMRI) research suggests that different components of cognitive control require different brain regions. Whilst the PFC is most active during the preparation period of each trial, indicating its role in maintaining attention, the Anterior Cingulate Cortex (ACC), a neighbouring brain region, is active during the response phase of each trial, suggesting it plays a role in conflict monitoring (MacDonald et al., 2000). A review of brain activity evidence shows that the ACC is critical for detection and correction of error in the Stroop and Flanker tasks (Bush et al., 2000) similarly suggesting the ACC is also a brain area critical for cognitive control. Critically, evidence suggests the ACC also has connections to the limbic system, important for emotion perception, response, and regulation. This suggests the ACC is critical for regulation of affect (Stevens et al., 2011). This evidence implies that the ACC would be active to successfully complete both the emotion regulation and cognitive control aspects of the Face Identification Task.

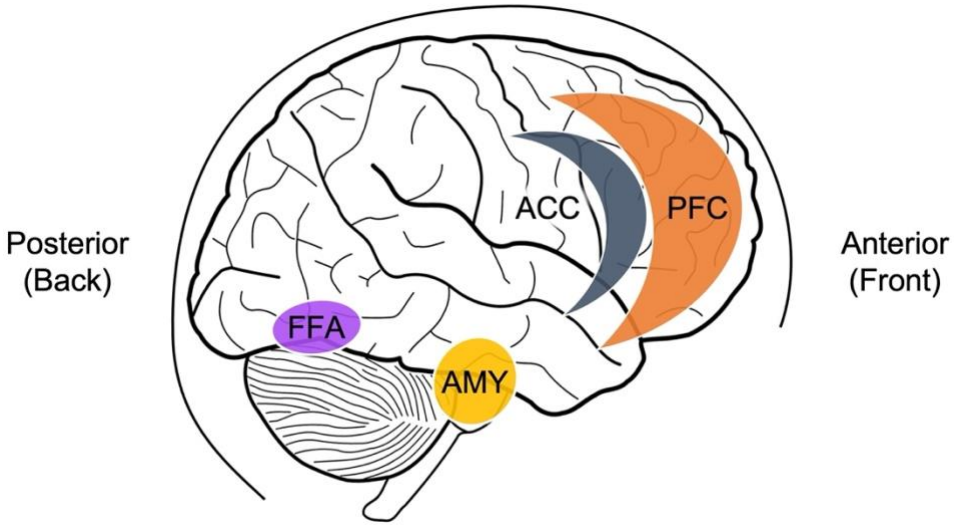
Multiple brain areas are needed to effectively process face stimuli. For example, the Fusiform Face Area (FFA) is implicated in the encoding of faces and face recognition (Kanwisher et al., 1997), and the Amygdala is implicated in determining the emotional states of others (Adolphs et al., 1995). (See Figure 5.4). Whilst there was no identified mediation effect of chronic pollution exposure group on socio-emotional processing in the current study (and acute DE exposure study in Chapter 4), it is clear that the Face Identification Task would activate brain regions such as the FFA and Amydgala which would otherwise not be necessary to complete a selective attention task without face stimuli.

The question therefore remains as to whether the identified results are reliant on the use of emotional face stimuli, or if this effect would still be present without. This is especially important considering the results from Chapters 2 and 3 which suggested that AP exposure can impact sensitivity to emotion expression. It is therefore critical to determine whether using emotional face stimuli puts extra strain on the limited brain resources required for high-level visual perception

and attention (Cohen et al., 2016) or if AP exposure is impacting brain areas relevant to face processing. Experiment 2 aims to do just this, by employing the same methodology as the current study with an executive function task that does not use socio-emotional stimuli.

Figure 5.4

Brain Regions implicated in effective Cognitive Control and Face Processing



Note. From posterior to anterior: FFA = Fusiform Face Area; AMY = Amygdala; ACC = Anterior Cingulate Cortex; PFC = Prefrontal Cortex

Experiment 2 – Chronic Air Pollution Exposure and Conflict Adaptation

Following the results of Experiment 1, the current study aimed to identify if AP causes a reduction in proactive cognitive control without the use of face stimuli, known to be highly compelling distractors, activating reactive control mechanisms (Langton et al., 2008). To tackle this problem, a Flanker Task, similar to that in Dodgson (2019), based on the same principles of the original flanker task (Eriksen and Eriksen, 1974), was used.

The Flanker Task differed from the Face Identification Task in that all trials contain stimuli distractors (flankers); trials are either congruent (target colour is the same as distractor colour; lower interference) or incongruent (target colour is the opposite of distractor colour; higher interference), as opposed to the Face Identification Task where trials were either one-face (scrambled distractor; lower interference) or two-face (face distractor; higher interference). Both tasks measure selective attention and efficiency of an individual to ignore distractors to focus on task goals. In this task, participants reported the colour of presented stimuli (orange or purple) rather than face gender, which would rely on brain areas responsible for face recognition (i.e., FFA and Amygdala) on top of those needed for cognitive control (i.e., PFC and ACC); see Experiment 1 discussion.

In the Flanker Task, Conflict Adaptation (CA) is often used as a measure of executive function (Botvinick et al., 1999; Egner, 2014). CA score indicates immediate reactive adjustment to current trial information considering congruency of preceding trials (Gratton et al., 1992). There are four two-trial sequence types to consider: congruent trials (trial *n*) where the preceding trial (trial *n*-1) was also congruent (cC); incongruent trials where *n*-1 was congruent (cI); congruent trials following incongruent (iC); and lastly incongruent trials following incongruent (iI). In general, current trial RT is faster following trials of the same congruency (cC and iI sequences), and slower when congruency is different between trial *n*-1 and *n* (cI and iC sequences). These relate to two congruency effects: Congruency Effect for trial *n* following a congruent trial *n*-1 [CE_{con} (cI minus cC)], and Congruency Effect for trial *n* following an incongruent trial *n*-1 [CE_{in} (iI minus iC)]. Conflict Adaptation score is the difference between these two congruency effects [CA (CE_{con} minus CE_{in})]. (See Table 5.4).

As above, reliance on information from the preceding trial is beneficial when the current trial is the same as the preceding trial (cC, iI) but will slow performance when the current trial is different from preceding (cI, iC). If attention disengagement from preceding trial information is

rapid, CE_{con} and CE_{in} will be similar indicating a limited role of previous trial on current trial performance, thus conflict adaptation effects are smaller. This results in more efficient performance over time as evidence suggests that task practice leads to less reliance on preceding trial type and in turn smaller conflict adaptation scores (Mayr and Awh, 2009; van Steenbergen, et al., 2015).

Table 5.4

Flanker Task Metric Definitions

Term	Definition
Congruent Trial	Target and flankers are the same colour
Incongruent Trial	Target is a different colour to flankers
Congruency Effect (CE)	RT for current incongruent trial (I) minus RT for current congruent trial (C)
CE_{con}	CE following a previous congruent trial (c)
CE_{in}	CE following a previous incongruent trial (i)
Conflict Adaptation (CA)	CE_{con} minus CE_{in}

A low conflict adaptation score is therefore indicative of better proactive control, whereby fast and accurate naming of the target colour regardless of preceding trial type shows better disengagement of attention between trials to focus on task goals. A higher conflict adaptation score indicates greater influence of preceding trial type on current trial performance, indicative of reactive control mechanisms capturing attention. Put simply, a lower conflict adaptation score is indicative of better proactive control.

It is hypothesised that performance on the Flanker Task will mimic that of the Face Identification Task in Experiment 1, as these are designed to measure selective attention within the umbrella of executive functioning processes. Specifically, those exposed to lower pollution concentrations across the lifetime will be better able to disengage attention from the preceding trial when responding to the current trial, indicating better proactive control compared to those exposed to higher chronic pollution, evidenced by lower conflict adaptation scores compared to their high pollution exposed counterparts.

Method

Participants

Sample sizes for this experiment were calculated based on the effect size obtained by van Steenbergen et al., (2010) who used a Flanker task with colour words (in Dutch) as flanker and target stimuli. In the study, participants were split into groups dependent on current mood and conflict adaptation score was compared between unpleasant (anxious / sad) and pleasant (calm / happy) groups. The current study is interested in the impact of chronic air pollution group (Low vs. High) on conflict adaptation score. From their results Cohen's d = 0.45 was calculated for conflict adaptation between groups (pleasant vs. unpleasant current mood). Therefore, Cohen's d = 0.45 and a power of 0.80 were assumed. The result was a required sample size of at least 80 participants in each group to observe an effect of condition (High vs. Low chronic pollution exposure) on conflict adaptation score, resulting in a total of 160 participants. Due to an estimate suggesting 8-25% of data from online studies is fraudulent or participants are inattentive (Jones et al., 2015) likely leading to data removal, an additional 35 participants (22%) were collected (total N = 195). G*Power 3.1 (Faul et al., 2007) was used for this analysis.

Undergraduate students at the University of Birmingham, Birmingham, UK were recruited through an online research portal and offered course credit on completion of the tasks. Individuals who reported current neurological, psychiatric, inflammatory, or respiratory disorders (e.g., multiple sclerosis, depression, rheumatoid arthritis, asthma), cold or flu symptoms in the past 14 days, vaccination within the last 14 days, or current smoking were excluded. As in Experiment 1, participants must have permanently resided in the United Kingdom from birth to present day to allow calculation of comparable lifetime pollution exposure scores.

Data from 195 students was collected. All data from 31 individuals were excluded from all analyses as they matched study exclusion criteria (N = 11), their depression score was +2.5SDs from overall means (N = 4), their anxiety score was +2.5SDs from overall means (N = 3), their sleep quality score was +2.5SDs from overall means (N = 3), and their accuracy on the task was below 80% (N = 10). Table 5.5 shows the characteristics of the remaining 164 participants.

Table 5.5

Demographic Characteristics of Chronic Pollution Exposure Experiment 2 Sample

Demographic Characteristic	All participants (*n* = 164)	Low Air Pollution (*n* = 83)	High Air Pollution (*n* = 83)	*p-value*	*t-value*
Mean Age (Years)	18.89 (*0.75*)	18.95 (*0.75*)	18.83 (*0.75*)	0.300	1.040
Sex (% Female)	85.98	80.72	89.16		
BMI (kg m^{-2})	22.22 (*3.81*)	22.25 (*3.17*)	22.19 (*4.39*)	0.923	0.097
Depression	7.71 (*7.80*)	7.34 (*8.07*)	8.07 (*7.56*)	0.550	-0.599
Anxiety	6.51 (*5.96*)	6.21 (*6.20*)	6.82 (*5.73*)	0.514	-0.654
Stress	11.84 (*8.35*)	11.33 (*7.95*)	12.34 (*8.75*)	0.439	-0.776
Sleep Quality (Overnight)	4.40 (*1.16*)	4.26 (*0.98*)	4.54 (*1.31*)	0.122	-1.555
Chronic Pollution Score	50.77 (*15.05*)	38.43 (*9.59*)	63.11 (*7.45*)		

Note: Standard deviation in parentheses. T-tests conducted between the Low and High chronic exposure conditions showed no significant differences among demographic characteristics at $\alpha = 0.05$ level.

Design

All procedures were approved by the University of Birmingham Science, Technology, Engineering, and Mathematics Ethical Review Committee (reference number ERN_18-0487). All methods were performed in accordance with relevant guidelines and regulations. This study used a between-participant quasi-experimental design. The naturally occurring between-subjects factor was chronic air exposure. Participants were split into a Low chronic pollution exposure group, or High chronic exposure group based on a median split. The median pollution exposure score was 52.35 (range: 11.05 – 74.05; interquartile range: 36.74 – 60.86). For reference, scores from Experiment 1 are highlighted here. [median: 55.36; range: 22.57 – 87.24; interquartile range: 42.77 – 65.14].

Materials

The Gorilla Experiment Builder (www.gorilla.sc) was used to create and host the questionnaires and Flanker Task online (Anwyl-Irvine et al., 2019). All other materials were the

same as Experiment 1 of the present Chapter without the ASQ due to the removal of emotional face stimuli. To measure proactive cognitive control the Flanker Task was used.

Flanker Task

Stimuli

Flankers were one of three Japanese Hiragana symbols, subtending approximately 1.9° x 1.4°, were presented in one of two colours, purple, RGB [123, 100, 123] #7b647b, or orange, RGB [199, 143, 0] #c78f00. See Figure 5.5 for example symbols. These symbols were used as they cannot easily be named by non-Japanese readers, inhibiting verbal encoding or activation of word-related mechanisms when presented. However, symbol shape was task-irrelevant, so not expected to interfere with task-goal or performance. The background colour was white, RGB [255, 255, 255] and explanatory text and fixation crosses appeared in black, RGB [0, 0, 0].

Procedure

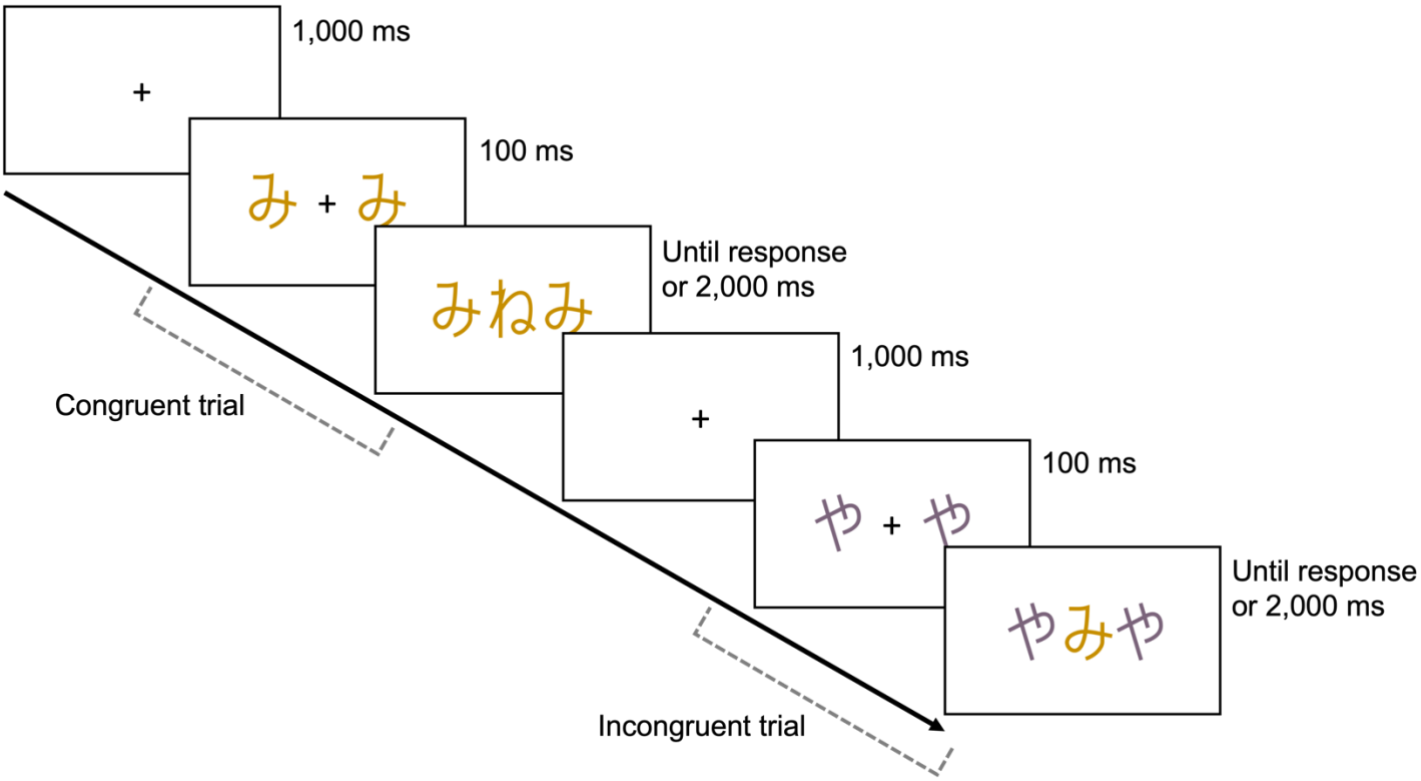
See Figure 5.5 for the sequence of displays in each trial. For each block participants were instructed to report the colour of the central target symbol ignoring the distracting flanker images. Participants responded as quickly as possible by pressing either the ‘k’ or ‘l’ keyboard keys for ‘purple’ or ‘orange’ (key meanings counterbalanced between participants) using the index and middle fingers on their dominant hand. Trials could be congruent (flanker and target colour matched) or incongruent (flanker was opposite of target colour). For each trial, a fixation cross was presented for 1,000 milliseconds (ms); followed by a brief presentation of the flanker symbols for 100 ms; lastly the target image appeared centrally between the flankers until participant response. After participant response or 2,000 ms the next trial would start. Eight blocks of 36 trials were presented, each containing an equal number of congruent and incongruent trials of each target colour.

The expectation in this task is that RTs are slower for incongruent trials as the flankers produce more interference than congruent trials. Critically, if an incongruent trial precedes another incongruent trial, interference is reduced on the current trial, producing comparatively faster RTs. This is thought to be due to strengthened cognitive control to overcome a similar, future conflict. Similarly, when congruent trials are preceded by incongruent trials, RTs are slower as the original

benefit of the lack of interference is reduced following the incongruency of the previous trial. These sequential changes are known as conflict adaptation (Gratton et al., 1992).

Figure 5.5

Illustration of the Flanker Task



Note. Each trial began with a fixation cross presented for 1,000 milliseconds (ms), followed by the flanker array for 100 ms, followed by the target array for until participants responded or 2,000 ms (counted as a missed trial). The task was to report the colour of the target (central symbol) as quickly as possible with a button press of 'k' or 'l' on the keyboard (counterbalanced between orange and purple). Symbols either side of the target (flankers) were to be ignored and would either be the same colour as the target (congruent trial) or the opposite (incongruent)

General Procedure

Participants were instructed to complete all tasks from a laptop or personal computer alone with no distractions such as mobile phones. Participants completed the DASS, PSQI, and PEL (See Chapter 2) questionnaires. Following this, participants took part in the Flanker Task (~20 minutes) and were debriefed and provided with course credit upon completion of all tasks.

Data Analyses

Flanker Task

All data from the first block was removed for all participants.

RTs were excluded from statistical analyses if there was no response, the response was too fast (RT < 200 ms), or the response was incorrect. First trial data from each block were removed, and individual RTs were trimmed if ±2.5 SDs from mean of sequence types: cC, cI, iC, and iI with the lowercase letter indicating congruency of the previous trial (c = congruent, i = incongruent) and uppercase letter indicating congruency of the current trial.

A 2x2x2 mixed ANOVA using trial *n*-1 congruency (congruent, incongruent) and trial *n* congruency (Congruent, Incongruent) as the repeated, and pollution group (Low Chronic Pollution Exposure, High Chronic Pollution Exposure) as the between factors was conducted on both RT and accuracy. Following the analysis, congruency effects were calculated [CE_{con} (cI minus cC) and CE_{in} (iI minus iC)] and entered into a 2x2 mixed ANOVA using congruency effect (CE_{con} and CE_{in}) as the within, and pollution group as the between factors.

Conflict Adaptation (CE_{con} minus CE_{in}) was also calculated for an independent-sample T-test comparing CA score for high and low pollution groups. Finally, a linear regression was conducted to identify the ability of lifetime air pollution exposure score to predict conflict adaptation score.

Results

Flanker Task

Response Time

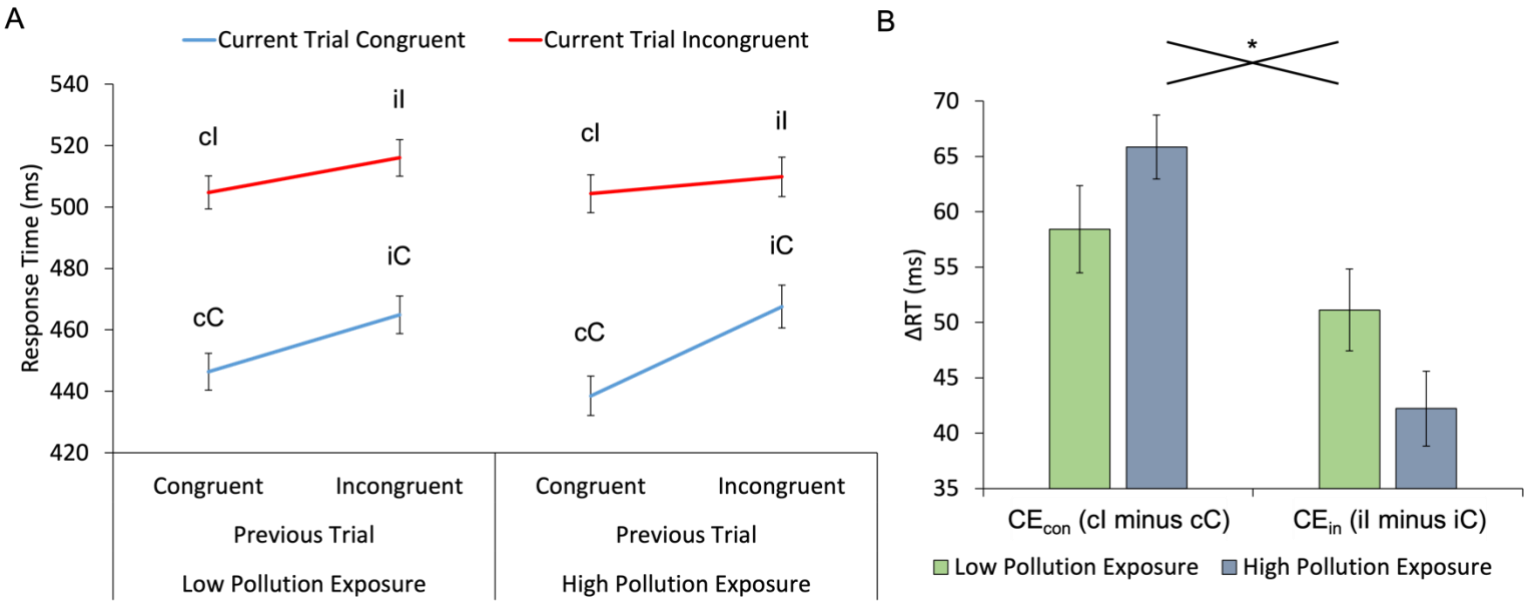
Firstly, an analysis of variance (ANOVA) of individual mean RT was used to compare previous trial (*n*-1) congruency (congruent, incongruent), current trial (*n*) congruency (Congruent, Incongruent) and chronic air exposure group (Low, High).

As expected, there was a main effect of current trial (*n*) congruency [$F(1, 162) = 697.574$, $p < 0.001$, $\eta p^2 = 0.812$, $1\text{-}\beta = 1$], such that RTs were faster when the trial was congruent (mean = 454 ms, s.d. = 59) compared to incongruent (mean = 509 ms, s.d. = 54). This effect was also seen for proceeding trial (*n*-1) congruency [$F(1, 162) = 120.984$, $p < 0.001$, $\eta p^2 = 0.428$, $1\text{-}\beta = 1$], such that RTs were faster on trial *n* when the proceeding trial was congruent (mean = 474 ms, s.d. = 63) compared to incongruent (mean = 490 ms, s.d. = 62). The interaction between these two, as expected, was also significant [$F(1, 162) = 31.413$, $p < 0.0001$, $\eta p^2 = 0.162$, $1\text{-}\beta = 1$] indicating that previous trial congruency mediated current trial RT dependent on current trial congruency. Importantly, the 3-way interaction between current and proceeding trial congruency and chronic pollution group was significant [$F(1, 162) = 8.733$, $p = 0.004$, $\eta p^2 = 0.051$, $1\text{-}\beta = 0.836$]. The interaction between chronic pollution group and current trial RT was non-significant, indicating that pollution group did not mediate single trial performance ($F < 1$). All other main effects and interactions were non-significant (*F-values* < 1). (See Figure 5.6A).

Following the results of the 2x2x2 ANOVA trials were collapsed into CE_{con} (cI minus cC) and CE_{in} (iI minus iC) for further analyses. As expected, there was a main effect of congruency effect [$F(1, 162) = 31.547$, $p < 0.001$, $\eta p^2 = 0.163$, $1\text{-}\beta = 1$], such that the congruency effect (RT incongruent current trial minus RT congruent current trial) was larger for congruent (mean CE_{con} = 62 ms, s.d. = 31) compared to incongruent (mean CE_{in} = 46 ms, s.d. = 32) preceding trials. There was no main effect of pollution exposure group ($F < 1$), however the interaction was significant [$F(1, 162) = 8.825$, $p = 0.003$, $\eta p^2 = 0.052$, $1\text{-}\beta = 0.840$]. (See Figure 5.6B). To explore this interaction effect, congruency effects (CEs) were collapsed into conflict adaptation (CA) scores (CE_{con} minus CE_{in}). An independent samples T-test identified that CA scores were higher in the High pollution group (mean CA = 24 ms, s.d. = 32) compared to the Low pollution group [mean CA = 7 ms, s.d. = 38; $t(162) = -2.971$, $p = 0.003$]. (See Figure 5.7A).

Figure 5.6

A: *Line Graph showing Mean RT (ms) for both Chronic Pollution Exposure Groups across Trial Type.* **B**: *Bar Chart showing Congruency Effects [CE_{con} (cI minus cC) and CE_{in} (iI minus iC)] for both Chronic Pollution Exposure Groups*



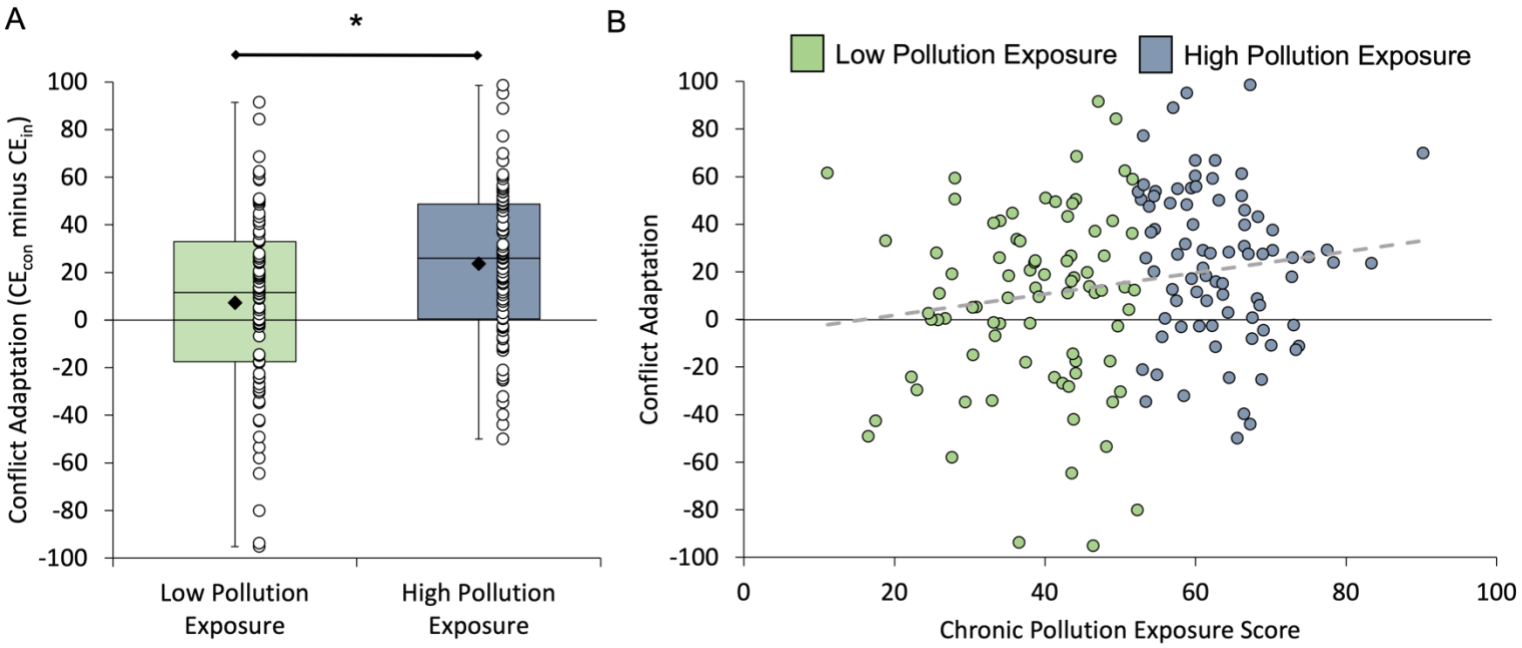
Note. **A**. Significant main effect of previous congruency, current congruency, and a three-way interaction between current and previous congruency and chronic pollution group. Error bars indicate standard error. **B**. Error bars indicate standard error. * indicates a significant interaction between pollution exposure group and congruency effect.

These results indicate that those exposed to lower concentrations of common air pollutants across the lifetime show enhanced disengagement of attention between trials, indicative of better task performance than those exposed to higher air pollution concentrations, where preceding trial congruency is more influential on current trial performance.

Lastly, a simple linear regression was used to examine the relationship between the predictor, chronic pollution exposure score, and the criterion, conflict adaptation. As in Experiment 1, despite a low amount of variance explained by the model (R^2 = 0.035), pollution exposure throughout the lifetime was a significant predictor of cognitive control, $F(1, 162)$ = 5.792, p = 0.017. There was a significant positive relationship between pollution exposure score and conflict adaptation score (T = 2.407, p = 0.017) with conflict adaptation increasing with increases in chronic pollution score. The model predicts that a 10 unit increase in pollution score would result in a conflict adaptation increase of 4.5 ms. (See Figure 5.7B).

Figure 5.7

A: *Boxplot showing Conflict Adaptation (CE_{con} minus CE_{in}) for both Chronic Pollution Exposure Groups.* **B**: *Scatterplot comparing Conflict Adaptation and Chronic Pollution Exposure Score*



Note. **A**: Upper and lower boxes show interquartile ranges, with central bar indicating median, and diamond indicating mean; circles indicate individual participants. The high chronic pollution group showed significantly lower conflict adaptation than the Low chronic pollution group [$t(59) = -2.454$, $p = 0.017$]. **B**: Green dots indicate those in the Low chronic pollution group and blue circles indicate High pollution group participants. There was a significant positive relationship between conflict adaptation score and pollution exposure [$F(1, 162) = 5.792$, $p = 0.017$]

Proportion Correct Scores

To identify if changes in participant accuracy could account for the similarities between air exposure group RTs and congruency effects, an analysis of variance (ANOVA) of individual mean proportion correct scores (%) was used to compare trial *n*-1 congruency (congruent, incongruent), current trial (*n*) congruency (Congruent, Incongruent) and chronic pollution group (Low, High).

There was a main effect of current trial congruency identified [$F(1, 162) = 104.596$, $p < 0.001$, $\eta p^2 = 0.392$, $1\text{-}\beta = 1$], with proportion correct higher on trial *n* when congruent (mean = 96.2%, s.d. = 3.7) compared to incongruent (mean = 93.1%, s.d. = 5.2). There was also an interaction between previous and current trial congruency identified [$F(1, 162) = 7.347$, $p = 0.007$, $\eta p^2 = 0.043$, $1\text{-}\beta = 0.769$]. No main effect of chronic pollution group or interaction was identified, indicating that pollution exposure mediated CA differences were not due to compensatory speed-

accuracy trade-off mechanisms. No other significant effects were identified [previous trial congruency: $F(1, 162) = 3.293$, $p = 0.071$; previous trial congruency and pollution exposure group interaction: $F(1, 162) = 1.943$, $p = 0.165$; other *F-values* < 1].

Air Quality Measures

Average chronic pollution exposure score was 63 ± (7) in the high exposure group and 38 ± (10) in the low exposure group. (See Figure 5.8A). As with the Experiment 1 (Face Identification Task) cohort, chronic pollution exposure score was highly positively correlated to average lifetime NO_X, $PM_{2.5}$, and PM_{10}. (See Table 5.6).

Table 5.6

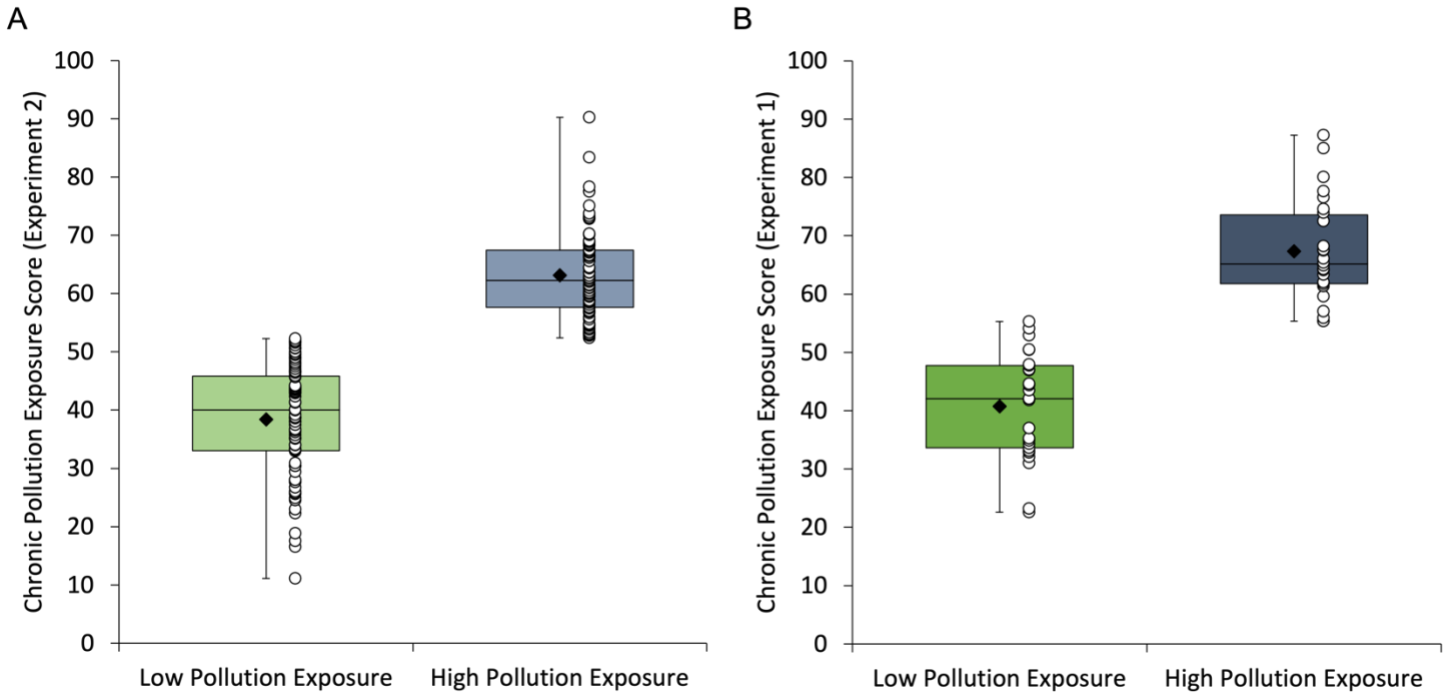
Comparison of Pollutant Concentrations and Chronic Exposure Score in Experiment 2

Pollutant	Low Air Pollution (*n* = 83)	High Air Pollution (*n* = 83)	All Participants (*n* = 164)	*r-value*		
				1	2	3
1. Chronic Pollution Score	38.43 (*9.59*)	63.11 (*7.45*)	50.77 (*15.05*)	—	—	—
2. NO_X ($\mu g\ m^{-3}$)	17.30 (*6.32*)	35.40 (*5.75*)	26.35 (*10.89*)	0.983	—	—
3. $PM_{2.5}$ ($\mu g\ m^{-3}$)	8.48 (*1.62*)	11.30 (*1.10*)	9.89 (*1.98*)	0.901	0.820	—
4. PM_{10} ($\mu g\ m^{-3}$)	12.65 (*2.75*)	16.41 (*1.47*)	14.53 (*2.90*)	0.883	0.788	0.915

Note. Values in parentheses indicate standard deviations. *r-value* indicates the correlation coefficient between pollutants and scores. Significant strong positive correlations were identified between all individual pollutants and pollutant exposure score (*p-values* < 0.001)

Figure 5.8

Boxplots showing between-group comparisons of Chronic Pollution Exposure Score in the **A**: *Current study (Experiment 2) and* **B**: *Experiment 1*



Note. Circles indicate individual participant mean scores with diamonds indicating group means

Discussion

In this study, participants' lifetime pollution exposure scores were used as a naturally occurring independent variable to form 'High' and 'Low' chronic pollution exposure groups using a median split. Conflict adaptation score were measured using a Flanker Task and compared between pollution exposure groups. Those in the high pollution groups showed higher conflict adaptation scores compared to those in the low exposure groups, indicating weaker proactive control following exposure to higher pollutant concentrations throughout the lifetime. Regression analyses indicated that chronic pollution exposure score was related to conflict adaptation, with higher chronic pollution exposure predicting higher conflict adaptation score and therefore poorer executive control.

The results of this study mimic those of Experiment 1, where participants exposed to higher pollutant concentrations throughout the lifetime showed lower proactive control, evidenced by higher ΔRT values on the Face Identification Task. This suggests that chronic exposure to high concentrations of AP is related to poor proactive control and that socio-emotional stimuli is not a requirement for this effect. It should be noted that the sample size was larger in this study (N = 165) compared to Experiment 1 (N = 51) to find an effect of a smaller size (Experiment 1, cognitive control between exposure groups: Cohen's d = 0.69; Experiment 2, conflict adaptation between exposure groups: Cohen's d = 0.48), indicating that using face stimuli enhanced the sensitivity of the task to identify executive function ability, most likely due to the super-distracting nature of faces (Langton et al., 2008).

One weakness of this experiment was that whilst normal vision was specified as inclusion criteria, colour-blindness was not actively assessed. Whilst there is no reason to suspect that those exposed to higher chronic AP were more likely to be colour-blind, this cannot be ruled out as a possibility. The removal of participants scoring below average 80% accuracy across all task trials (including one participant who self-reported perceiving purple stimuli as black) ensured that only participants engaged in the task and performed well above chance level (50%) were included in the analysis. In future, a colour-blindness test, e.g., the Farnsworth-Munsell D-15 colour vision test, should be used to ensure this is not a confounding factor.

Whilst all participants in Experiment 1 travelled from within Birmingham to the testing location, the online nature of the task in Experiment 2 meant that participants completed the task from multiple locations within the UK (although the majority within Birmingham). This has

implications for the validity of the results following evidence that acute exposure also alters attentional processing (Chapters 2, 3, and 4). However, Comparing the results of Chapter 4 showed that acute DE exposure caused a reduction in cognitive control regardless of chronic pollution exposure, indicative that acute high exposure episodes may supersede the effect of chronic exposure.

As chronic exposure is the product of a lifetime of acute exposure episodes, it could be that continued acute exposure leads to neural degeneration, as evidenced by a negative association between high chronic AP exposure and PFC volume (Gale et al., 2020). With the exact mechanisms of the identified effect unknown, one key avenue for future exploration is the relative impact of acute vs. chronic AP exposure on cognitive control. To investigate this, a longitudinal paradigm could assess cognitive control on a yearly basis measuring both recent (24-hour) pollution concentrations and annual exposure. Across time, linear statistical modelling could provide the relative impact of chronic vs. acute exposure on cognitive control providing insight into the interaction between the two. Including both functional and structural brain imaging methods within a longitudinal design could also provide indication of the mechanistic underpinnings of the identified effect, i.e., reduction in structural volume of brain regions critical for attention modulation, e.g., AAC and PFC, or simply lower functional activity in these areas during selective attention tasks.

The key implication of the identified degradation of cognitive control related to chronic AP exposure evidenced in Experiments 1 and 2 is the importance of executive function in rational decision making (Diamond, 2013). Cognitive control is critical in human adaptation to ever-changing environments and maintaining goal-directed behaviours (Ionescu, 2012), critical for human survival. There is evidence that poorer cognitive control is associated with risky behaviour in adolescents (Rodrigo et al., 2014), with similar neural pathways implicated to that of cognitive control. This may imply that those exposed to AP have poorer decision making processes leading to risky behaviour which could be tentatively linked to the reduction in pro-social behaviour identified in Chapters 2 and 3. As well as this, there is evidence that poor cognitive control is associated with mental health disorders (Gabrys et al., 2018) potentially indicating that poorer cognitive control presents a risk factor for development of affective disorders such as anxiety and depression, which have themselves been associated with exposure to high AP concentrations (Gładka et al., 2018; Power et al., 2015).

Chapter 6 – General Discussion

General Discussion

The main aim of this thesis was to identify the impact of both acute and chronic air pollution exposure on a range of cognitive functions in a young adult population. With the literature heavily focused on the effects of chronic pollution exposure on both the developing (Calderón-Garcidueñas and Mora-Tiscareño et al., 2008) and aging (Calderón-Garcidueñas, 2002) brain, it was fundamental to identify effects for clinically healthy adults as they are also exposed to indoor and outdoor sources of air pollution throughout their daily lives (Samet et al., 1987; Khreis, 2020). This is particularly critical as healthy adults form the largest working cohort in society, therefore socioeconomic development relies on their optimum cognitive performance. The literature surrounding the effects of acute air pollution exposure is sparse and often conflicting, providing limited mechanistic explanations for any identified effects (Bos et al., 2013; Saenen et al., 2016; Shehab and Pope, 2019; Gao et al., 2021). In this thesis, it is demonstrated that acute air pollution exposure causes reduction in complex cognitive functions such as cognitive control (Botvinick et al., 1999; Egner, 2014) and social-emotion cognitive biases, but not episodic memory recall, advancing this novel field by identifying specific cognitive functions most at risk from AP exposure. Most identified effects occurred following a time delay between pollution exposure and changes in behavioural outcomes, mimicking previous research investigating sickness behaviour (Balter et al., 2018; Balter et al., 2019). This helps builds confidence that inflammatory mechanisms are the most likely explanation for the identified effects. Evidence in favour of this conclusion is summarised below. The impact of these findings has implications for quality and ease of decision making (Diamond, 2013) and emotional control, potentially degrading mental health.

Summary of studies

To investigate the impact of acute air pollution exposure on cognitive function, both experimental (Chapters 2 and 4) and quasi-experimental (Chapter 3) methods were used with emphasis on particulate matter (Chapter 2) and traffic-related air pollution (Chapters 3 and 4) exposures. Chronic pollution, including regional-scale and traffic-related pollution at 1 km^{-2} resolution, was also assessed (Chapter 5) to identify similarities between acute and chronic effects. Social-emotional cognition (Emotional Discrimination Task: Chapters 2 and 3), executive function

(Face Identification Task: Chapters 4 and 5; Flanker Task: Chapter 5), and spatiotemporal episodic memory (Memory Arena: Chapters 2 and 3; Memory Task: Chapter 4) were the core cognitive components investigated. These were chosen based on prior evidence of attentional, socio-emotional and memory dysfunction in previous research coupled with knowledge of brain activity changes in frontal regions following acute exposure episodes and non-pollution related vaccination paradigms.

Key psychological measures derived from the experimental data were:

Approach bias: A prepotent behavioural inclination to approach positive-affective and avoid negative-affective stimuli.

Spatiotemporal episodic encoding: The ability to store information about the sequence and location of a set of novel objects.

Cognitive control and Conflict adaptation: The ability to remain goal-orientated (on-task) by ignoring the influence of task-irrelevant distractions though strategic modulation of attention.

In Chapter 2, the aim was to identify if acute air pollution exposure caused changes in social-emotional cognition, namely Approach bias, and spatiotemporal encoding and retrieval of episodic memory. To investigate, participants were exposed to either high PM concentrations via candle burning, or clean air. Participants learned and recalled the sequence and location of 20 object images (Memory Arena; Petzka et al., 2021), then completed a Go/No-go task with emotion expression as target classifier (Emotional Discrimination Task). 24 hours later spatiotemporal memory recall and the Emotional Discrimination Task were tested once more. Whilst there were no differences in encoding and recall ability between the pollution exposure groups, the Clean Air group showed an increase in Approach bias 24 hours after exposure compared to the Candle group who showed a reduction in Approach bias. These results indicated a reduction in pro-social behaviour 24 hours after exposure to high PM concentrations. As group differences were only identified 24 hours following exposure, this result may be indicative of inflammatory agents initiating sickness-related social withdrawal (Eisenberger et al., 2010).

To identify if these effects replicated after exposure to real-life ambient sources, Chapter 3 used a similar procedure with natural-experimental exposure to TRAP as the quasi-independent variable. High and Low TRAP exposure groups were created using a median split of the participant

average PM_{10} concentrations during commute to the study. As in the experimental exposure study (Chapter 2), the Memory Arena and Emotional Discrimination Task were administered immediately following commute, and 24 hours later. Emotional Discrimination Task performance mirrored that of the experimental exposures in Chapter 2, whereby Approach bias decreased 24 hours after commute in the High pollution group but increased in the Low pollution group. Data was pooled between the studies in Chapters 2 and 3; a linear regression showed that average PM_{10} concentration predicted Approach bias 24 hours later. Evidence suggests a strong connection between brain areas involved in social-emotional and executive processing (Adolphs, 2009). Therefore, a reasonable explanation for these effects is reduction in top-down (executive) processing (Mohanty and Sussman, 2013) due to pollution-mediated inflammation. Those in the High polution group showed deficits in spatiotemporal encoding immediately following commuting compared to the Low exposure group, a pattern differing from the null results in the experimental manipulation in Chapter 2. With inflammation unable to account for immediate effects, acute hypoxia (MacIntyre, 2014) is an alternative explanation. The difference between study results may be due to higher concentrations of compounds that compete with O_2 for haemoglobin abundant in TRAP (Wróbel et al., 2000) but not candle burning, providing more potential for hypoxic events. However, task-related confounding factors, notably individual differences related to encoding strategies (Kirchhoff, 2009) were not controlled for.

Following the indication that the Approach bias effect may be related to changes in top-down processing, an executive function with a task-irrelevant social cognition element was created (Face Identification Task) for future investigations. In Chapter 4, participants were exposed to Diesel Exhaust (DE) or Clean Air for one hour. Participants then either performed the Face Identification Task and Memory Task immediately or 4 hours following the end of exposure. Lower cognitive control (Egner and Hirsch, 2005) ability was identified after exposure to DE compared to clean air 4 hours following exposure, but no differences were identified in those tested immediately. Once again, inflammatory mechanisms best explained these effects with previous studies identifying attenuated attention 6-hours following vaccination (Balter et al. 2019; Allison and Ditor, 2014). Whilst cognitive control is a measure of executive function (Botvinick et al., 1999; Egner, 2014), the use of emotional faces as distractors may have heightened effects, therefore not indicative of performance on common cognitive control paradigms such as the flanker task (Eriksen and Eriksen, 1974). Pollution exposure group did not mediate differences in

spatiotemporal episodic memory when encoding strategy (Kirchhoff, 2009) was controlled, possibly suggesting the effects identified in Chapter 3 were not pollution mediated.

Finally, chronic pollution exposure was estimated using participant residential postcodes from birth through to present day for two separate cohorts (Chapter 5). Participants were split into High and Low chronic pollution groups using a median split in each cohort and took part in either the Face Identification Task or Flanker Task (which did not use face stimuli; Dodgson, 2019). Higher chronic pollution exposure predicted lower proactive cognitive control ability in both tasks, indicative of poorer executive function ability (Gratton et al., 1992). These results paralleled the identified reduction in cognitive control following acute DE exposure in Chapter 4, indicating that similar cognitive abilities are attenuated by both acute and chronic pollution exposure. As effects were stronger for participants completing the Face Identification Task in comparison to the Flanker Task, this may indicate that the use of expressive face stimuli strengthened distractibility (Langton et al., 2008).

Theoretical summary

To explain the range of findings highlighted, see Figure 6.1 for an informal theoretical diagram. Based on the evidence presented in this thesis, inflammation is a likely mechanism to explain the delayed effect of acute AP exposure on both Approach bias and cognitive control. Assuming the same mechanism for the identified effects, it is reasonable to assume that a reduction in pro-social behaviour would also be prevalent 4 hours following an acute high TRAP exposure episode, with the same true for cognitive control 24 hours later. Whilst both the duration between AP exposure and cognitive dysfunction and the longevity of the effect are unknown, the evidence presented suggests that executive dysfunction is identifiable 4 hours following exposure and persists for at least 20 hours from this point (24 hours following exposure end).

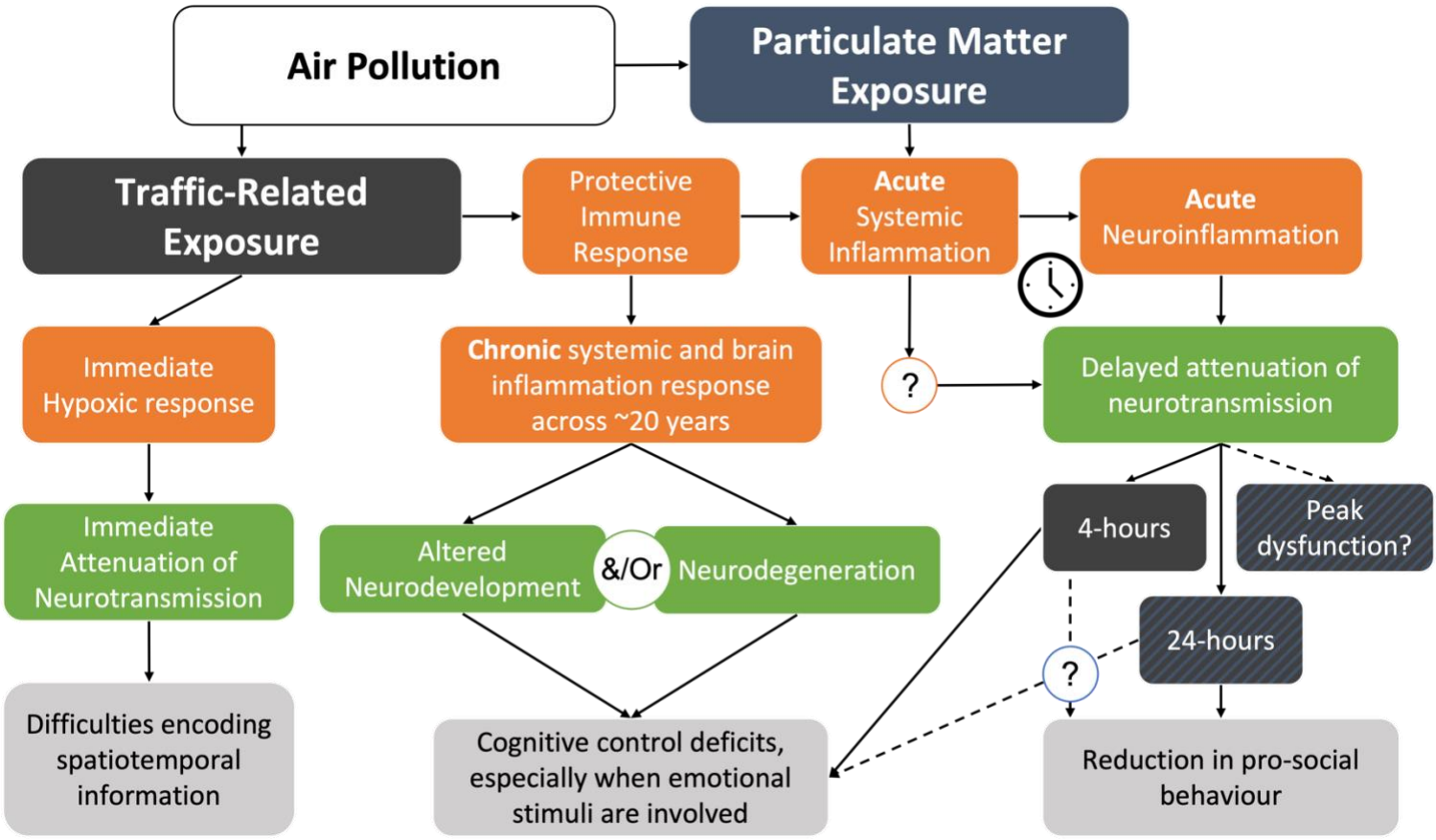
Based on evidence identifying inflammatory changes following chronic AP exposure, this mechanism is also implicated in the dysfunction of cognitive control following high exposure to chronic AP. However, it remains unknown whether these results are due to neurodegeneration following chronic exposure (as suggested in older adult populations), or through changes in neurodevelopment (as suggested in studies of children).

The immediate effect of TRAP exposure on episodic encoding is also highlighted within this thesis. This is assumed to be TRAP specific as the effect was not identified when using a

candle to generate PM. TRAP contains oxygenated-radicals, resulting in a hypoxic response whereby oxygen saturation is lower than normal in the body and therefore brain. This in turn attenuates neurotransmission required for the encoding of novel information, critically this effect only relates to learning of information, not retrieval, and not any attentional mechanisms.

Figure 6.1

Diagram summarising Identified Effects and their Likely Mechanisms



Note. Orange indicates suggested causal effect of AP exposure. Green indicates the impact of orange processes on brain function / structure. Light grey indicates cognitive dysfunctions

Future research

The studies in this thesis have added to a field of relative infancy with a targeted focus on appropriate behavioural testing. Understandably, several queries still remain regarding the impact of air pollution exposure on cognitive function which were unable to be investigated within this thesis.

Firstly, it was assumed for the purposes of this thesis that exposure was indicative of pollutant dosage. Whilst all studies excluded participants with respiratory conditions, including asthma, individual differences in lung function will result in individual differences in pollution dose. Of particular concern are sex differences in lung function and therefore inhalation volumes, although participant size may be more indicative than sex (LoMauro and Aliverti, 2018). In future, studies should attempt to recruit equal numbers of males and females and measure lung function via measures such as peak expiratory flow rate and forced expiratory volume (Dimech and Sturman, 2011) to regress into analyses. This would account for pollution dose as a confounding variable in future human exposure studies.

Another confounding factor in the outlined experiments was a lack of air quality measures between exposure and testing. Whilst information was collected regarding possible high-exposure activities between testing sessions, the true effects of participant exposure to other pollutant concentrations outside the lab are unknown. In future, participants could be kept under observation during the time between exposure and testing to account for erroneous pollutant exposure between testing periods. This would be made possible, even for overnight studies, using sleep labs. Alternatively, portable pollution monitors as used in the natural TRAP exposure study would be a low-cost solution for estimating personal pollutant exposure between testing periods.

One critical question remaining following the evidence presented in this thesis is the relative contribution of different pollutant-species to cognitive dysfunction. As humans are exposed to air pollution both indoors and outdoors throughout the day, often above legal limits (Hammer et al., 2020; Nezis et al., 2019), identifying the relative toxicity of each pollutant-species and different impacts on brain function is imperative. Whilst some pollutants co-vary strongly, a combination of repeated exposures to different pollutant sources along with physiological measures and biological sampling may allow for the dissociation between pollutant-species, inflammatory response, and cognitive effects. Crucially, this could inform policy for reduction in pollutant-species most relevant to human cognitive dysfunction and/or decline.

Whilst previous literature has identified changes in resting-state EEG both during (Crüts et al., 2008) and following (Driessen et al., 2012; Naseri et al., 2019) air pollution exposure, the behavioural implications of these measures are limited. Applying function-specific event-related potential (ERP) analysis (Luck, 2005) along with executive function tasks would provide more detailed picture of the implications of air pollution exposure on brain function. Critically, this

method would allow for conclusions to be drawn between specific cognitive functions and air pollution exposure even when behavioural effects are not present, as in Balter et al., (2019). Following the identified delayed effects of AP exposure on executive functioning, targeted ERP testing could reveal important distinctions to aid further understanding of these effects, i.e., hemispheric differences in prefrontal areas during a cognitive control task.

The studies in this thesis highlight a reduction in Approach bias 24 hours following air pollution exposure and reduction in cognitive control 4 hours following air pollution exposure. Whilst both results are indicative of inflammation as the mechanistic explanation of these effects, both the peak and longevity of the identified effects remain unknown. Repeated cognitive testing across a short time period may allow detection of these factors, although measures would need to be robust in the face of learning effects.

Implications

Approach bias tendencies can be critical for threat avoidance, and dysregulation of these tendencies (as seen as a result of air pollution) is linked to both social withdrawal and aggressive behaviours (Kaldewaij et al., 2016). If the identified effects implicate social withdrawal this potentially has wide ranging impacts for the development of affective disorders such as depression, already implicated as a result of air pollution exposure (Gładka et al., 2018). If the identified effects indicate an increased propensity of aggressive behaviour, air pollution exposure may cause a rise in antisocial behaviour and violent tendencies. This finding may explain air-pollution-related increases in violent crime in Chicago and Los Angeles metropolitan area (Herrnstadt et al., 2016), although heat and humidity in these regions may also play a role.

Cognitive control ability is crucial for the completion of tasks requiring sustained attention in the face of distractors (Botvinick et al., 1999; Braver, 2012). The identified reduction in cognitive control after AP exposure may therefore indicate a reduction in behavioural efficiency. This result could explain extant evidence linking AP exposure to a loss of productivity (Wyon, 2004) as well as stock returns (Levy and Yagil, 2011), indicating the possible economic consequences of these attentional deficits.

The most important tactic to avoid AP-related cognitive deficits is to reduce pollution concentrations or reduce human exposure to high pollutant concentrations. However, given the ubiquity of AP in urban regions and lack of individual control over pollutant concentrations

experienced, there are other strategies which may mitigate the negative cognitive effects following high-exposure episodes such as commuting. Working from home (assuming appropriate ventilation and avoidance of high pollution behaviours, such as candle burning) could alleviate most if not all cognitive dysfunction related to AP exposure. Similarly, if work cannot be completed from home, employers should ensure that air quality within office spaces is as clean as possible. Follow-up research to identify the peak of cognitive dysfunction following AP exposure could identify the best time for employees to take breaks to achieve maximum productivity.

In conclusion, this thesis has provided evidence that acute manipulated and naturally-occurring experimental exposure to traffic-related air pollutants causes a reduction in pro-social behaviours and cognitive control ability, with a similar pattern of effects identified in those exposed to higher pollution concentrations throughout the lifetime. Critically, the identified effects occur in clinically healthy adult populations, relatively unstudied within the field. The most plausible explanation for the identified effects is inflammatory agents initiating cognitive deficits without other classic symptoms of sickness behaviour.

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Supplementary Materials

Appendix A:

Characteristic	Time	Immediate Testing		Delay Testing		Comparison	Group		Time		Interaction	
		Clean Air (n = 19)	Diesel Exhaust (n = 19)	Clean Air (n = 22)	Diesel Exhaust (n = 21)		*p*	BF_{excl}	*p*	BF_{excl}	*p*	BF_{excl}
0 = Tense 100 = Relaxed	Pre-Exposure	60.60 (*24.64*)	53.94 (*25.92*)	62.85 (*25.67*)	70.27 (*26.74*)	All Groups	0.297	3.975 **	0.006 *	0.324	0.179	3.487 **
	Immediately post-Exposure	68.09 (*20.95*)	72.14 (*21.55*)	63.39 (*24.87*)	76.24 (*19.82*)							
	4 hours post-Exposure			74.98 (*17.64*)	72.92 (*20.67*)	Delay Groups	0.278	2.455	0.136	2.949	0.120	3.607 **
0 = Irritated 100 = Calm	Pre-Exposure	71.88 (*22.36*)	68.80 (*21.20*)	71.70 (*21.60*)	78.84 (*18.15*)	All Groups	0.498	8.210 **	0.396	5.891 **	0.656	68.435 **
	Immediately post-Exposure	68.75 (*20.47*)	72.16 (*21.60*)	67.54 (*19.96*)	74.54 (*17.14*)							
	4 hours post-Exposure			76.61 (*15.19*)	74.57 (*20.74*)	Delay Groups	0.382	3.194 **	0.229	5.037 **	0.212	9.363 **
0 = Excited 100 = Bored	Pre-Exposure	42.24 (*13.60*)	38.09 (*17.94*)	42.65 (*17.55*)	39.96 (*16.19*)	All Groups	0.855	16.035 **	0.001 *	0.056	0.968	43.049 **
	Immediately post-Exposure	50.34 (*19.99*)	47.06 (*15.56*)	48.58 (*18.02*)	48.10 (*21.18*)							
	4 hours post-Exposure			43.50 (*18.72*)	42.89 (*20.01*)	Delay Groups	0.779	4.232 **	0.058	1.657	0.929	15.639 **
0 = Happy 100 = Sad	Pre-Exposure	34.10 (*22.63*)	29.27 (*16.46*)	30.76 (*18.38*)	23.58 (*20.55*)	All Groups	0.828	6.598 **	0.016 *	0.509	0.162	5.417 **
	Immediately post-Exposure	34.07 (*20.31*)	31.99 (*18.90*)	34.77 (*19.24*)	35.02 (*20.16*)							
	4 hours post-Exposure			35.81 (*20.59*)	32.02 (*17.59*)	Delay Groups	0.497	2.451	0.004 *	0.191	0.315	2.903

Supplementary Table 1: Mean reported mood in each group across all timepoints (s.d. in brackets): * indicates $p < .05$, ** indicates $BF_{excl} > 3$. Frequentist analysis indicated no effect of exposure group or interaction between air exposure and time for any of the reported mood measures.

Appendix B:

Side effect	Time of reporting	Immediate Testing		Delay Testing		Group Comparison	Group		Time		Interaction	
		Clean Air (n = 19)	Diesel Exhaust (n = 19)	Clean Air (n = 22)	Diesel Exhaust (n = 21)		*p*	BF_{excl}	*p*	BF_{excl}	*p*	BF_{excl}
Effect on Cognition	Immediately	4 (*21.05*)	4 (*21.05*)	5 (*22.73*)	3 (*14.29*)	All	0.911	12.195 **				
	4-hour delay			3 (*13.64*)	2 (*9.52*)	Delay	0.525	3.151 **	0.190	2.749	0.680	7.986 **
Headache	Immediately	5 (*26.32*)	6 (*31.58*)	6 (*27.27*)	6 (*28.57*)	All	0.986	14.020 **				
	4-hour delay			4 (*18.18*)	6 (*28.57*)	Delay	0.592	4.126 **	0.582	5.342 **	0.582	12.325 **
Dizziness	Immediately	6 (*31.58*)	7 (*36.84*)	10 (*45.45*)	7 (*33.33*)	All	0.802	10.366 **				
	4-hour delay			5 (*22.73*)	6 (*28.57*)	Delay	0.804	3.178 **	0.059	1.164	0.211	3.191 **
Nausea	Immediately	1 (*5.26*)	1 (*5.26*)	0 (*0.00*)	0 (*0.00*)	All	0.522	6.690 **				
	4-hour delay			0 (*0.00*)	1 (*4.76*)	Delay	0.312	3.490 **	0.312	3.524 **	0.312	6.739 **
Fatigue	Immediately	9 (*47.37*)	4 (*21.05*)	9 (*40.91*)	7 (*33.33*)	All	0.372	4.952 **				
	4-hour delay			9 (*40.91*)	6 (*28.57*)	Delay	0.451	3.085 **	0.740	5.972 **	0.740	14.057 **
Shortness of breath	Immediately	5 (*26.32*)	7 (*36.84*)	6 (*27.27*)	7 (*33.33*)	All	0.881	11.697 **				
	4-hour delay			1 (*4.55*)	3 (*14.29*)	Delay	0.439	2.873	0.002 *	0.068	0.773	2.919
Coughing	Immediately	0 (*0.00*)	3 (*15.79*)	5 (*22.73*)	1 (*4.76*)	All	0.084	1.323				
	4-hour delay			2 (*9.09*)	2 (*9.52*)	Delay	0.281	2.290	0.433	3.901 **	0.109	3.095 **
Throat irritation	Immediately	2 (*10.53*)	0 (*0.00*)	2 (*9.09*)	3 (*14.29*)	All	0.447	5.823 **				
	4-hour delay			3 (*13.64*)	4 (*19.05*)	Delay	0.562	3.762 **	0.426	4.575 **	0.985	13.467 **
Uncomfortable feeling	Immediately	1 (*5.26*)	3 (*15.79*)	6 (*27.27*)	5 (*23.81*)	All	0.291	3.933 **				
	4-hour delay			1 (*4.55*)	2 (*9.52*)	Delay	0.936	3.400 **	0.004 *	0.199	0.489	2.912

Supplementary Table 2: Number of participants reporting each side effect in each group alongside the percentage in brackets: * indicates $p < .05$, ** indicates $BF_{excl} > 3$. Frequentist analysis indicated no effect of group on reported side effects immediately with Bayesian analysis confirming the null hypothesis for all but reported coughing. Frequentist analysis indicated no main effect of exposure group or interaction between group and time for the delay groups. Significant main effect of time for shortness of breath and generic uncomfortable feeling, with less participants reporting these side effects 4 hours after exposure compared to immediately.