Study protocol

Effect of Air Pollution on the Cognitive Function of Adolescents (ATENC!Ó)

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STUDY PROTOCOL

Study Protocol, drafted by the Sponsor, ISGlobal, through the Principal Investigator, Xavier BASAGAÑA, hereinafter referred to as "Sponsor" or "we".

Summary:

The scientific objective of this project is to study whether atmospheric pollution in high schools can affect the adolescents' attention processes and their decision making with respect to risk, time and social considerations. The confirmation of this relationship is useful for designing prevention strategies with a great potential for benefits for society, since attention is closely linked to learning and academic performance. The main innovation of the project is its experimental design, as opposed to the existing evidence that comes from observational studies. High school students in 3rd grade (ESO, 14-15 years of age) in different high schools in the Barcelona province (Spain) will be invited to participate. For each class in each high school, participating students will be randomly split into two equal-sized groups. Each group will be assigned to a different classroom where they will complete several activities during two hours, including an attention test (Flanker task) and a reduced version of the Global Preferences Survey. One of the classrooms will have an air purifier that will clean the air. The other classroom will have the same device but without the filters, so it will only re-circulate the air without cleaning it. Students will be masked to intervention allocation. The investigators hypothesize that students assigned to the clean air classroom will have better scores in the attention test, and that decision-making will also present differences in the two classrooms.

Introduction

Recent evidence is showing that air pollution can affect the brain, both in epidemiological studies and in animal or post-mortem studies, which have detected the presence of particles from traffic origin in the brain (Block et al., 2012). For the specific case of studies in children, it has been reported that living in places with higher levels of traffic pollution is associated with poorer cognitive function, worse scores in behavioral tests and slower neuropsychological development. Our team recently performed the first study that linked the levels of pollution in schools with the cognitive development of children between 7 and 10 years of age (Sunyer et al., 2015). This study showed that children who attend schools with higher levels of air pollution had a slower cognitive development (7% annual gain) than those who go to schools with lower levels of air pollution (12% annual gain). This corresponded to a delay in cognitive development of about 5 months. Analyzing the particles sampled in the filters, the study concluded that particles from the traffic were the only ones that affected neurodevelopment (Basagaña et al., 2016). Apart from assessing the effect of being chronically exposed to high levels of air pollution, the study also found that the results of attention tests were worse in days with higher air pollution (Sunyer et al., 2017), suggesting that an acute effect of air pollution on attention is also possible.

So far, most studies linking air quality in schools and academic performance and the existing recommendations for air quality in schools only focus on CO_2 levels. High levels of CO_2 indicate poor ventilation, and it is known that high levels are associated with poorer attention, memory and concentration (Barrett et al., 2015). However, CO_2 is not considered an environmental contaminant, since it is not associated with health problems at the levels found in buildings. Traffic contamination, on the other hand, is associated with various health problems, including changes in the functioning of the brain in children (Sunyer et al. 2015; Pujol et al. 2016). Current guidelines recommend good ventilation in schools, which is carried out naturally in most schools in Spain by opening windows. Although this is effective in reducing CO_2, it can cause the infiltration of traffic pollution, as it was observed recently in our study in Barcelona (Rivas et al., 2015), since many schools are very close to traffic.

The main limitation of the existing studies relating air pollution and cognitive development is that they are observational studies and therefore they are subject to potential residual confounding. For example, children who attend more polluted schools may have a different socioeconomic profile than those who go to schools with lower levels, and that may explain part of the effects attributed to air pollution. One way to avoid these biases is to carry out randomized experiments. Until recently, experiments of this type had been restricted to studies in specially prepared exposure chambers. With the emergence of mobile air purifiers, some studies have been conducted in real life conditions. For example, a study in China conducted an experiment in which an air purifier was installed in half of the student dorms of a student residency for two days in a crossover study (Chen et al., 2015). Particle levels significantly decreased with the purifier, and in the days when the purifier was in use, improvements were detected in various health parameters such as levels of inflammatory biomarkers. In terms of cognitive function, we only know the existence of an experimental study in Denmark, which conducted a randomized experiment with an air purifier involving 190 children aged 10 to 12 (Wargocki et al., 2008). In a crossover trial, children were exposed for a week to filtered air and for another week to non-filtered air. The study did not find differences in the scores of two math tests and reading, but they found some improvements in the speed to complete the test.

Attention processes are an interesting option to study the effects of air pollution with experiments, as they can fluctuate within the same day and are susceptible to the effects of environmental variables. Attention processes are essential complex cognitive functions for learning that include alerting, or ability to have and maintain vigilance during a task; the orientation, which involves shifting the attention from one stimulus to another when required; and executive attention, which involves detecting and resolving conflicts between responses, detecting errors or inhibiting responses. Our previous observational study was the first to investigate the relationship between exposure to air pollution and changes in attention in the short-term (within 24 hours) (Sunyer et al., 2017). An experimental study in 10 adults detected changes in frontal cortex activity, related to atttention processes, 30 minutes after starting exposure to air pollution (Crüts et al., 2008), which supports the hypothesis that the effects of air pollution can occur quickly.

There exists a very recent economic literature showing that the variability among individuals in their cognitive functions is an explanatory factor on the variability in their preferences with respect to time and risk (Dohmen et al 2010; Proto et al, forthcoming). Hence, there exists the potential that air pollution may also affect individual preferences on risk and time, as well as on social considerations, like reciprocity and trust. These three elements (time, risk and social considerations) are essential in the understanding of individuals' decision-making process, and hence lie at the core of the economic analysis. However, there are no controlled experiments that have studied the direct effect of air pollution on economic decision-making.

Hypotheses and objectives

The objective of the study is to evaluate the attention of students exposed to purified air (low pollution) and those exposed to the metropolitan area of Barcelona (high pollution) levels through an experiment Randomized with air purifiers, and compare the results. The hypothesis is that exposure to contamination worsens the attention of students.

The objectives of the study are to identify if cleaning the air of a classroom has an impact on:
1) The attention of high-school students

2) The individual preferences with respect to risk, time and social considerations

The investigators hypothesize that students assigned to the clean air classroom will have better scores in the attention test, and that decision-making will also present differences in the two classrooms.

Study Design

Participants and recruitment

The subjects of study will be students of 3rd grade (ESO) of high schools of the metropolitan area of Barcelona that accept to participate in the study. The participating high schools will distribute informed consent forms so that both the students and their parents or legal guardians sign it as an agreement to participate in the study. Only students with the signed informed consent will participate.

Experiment

This is a randomized experiment that will link air pollution levels with attention processes and decision making of the participants. The experiment will randomly split each class of maximum 30 students into two groups. Each group will go to a different classroom (but equivalent in size, orientation and windows) to perform the same activities for a duration of two hours.

The two classrooms will have an air purifier (Pure Airbox, Zonair 3D, capable of filtering the entire air of a 45 m^2 room every 10 minutes). The air cleaner in one of the rooms will have the filters installed, and thus will clean the air, while the air cleaner in the other classroom will not have the filters installed, and therefore it will simply recirculate the air without filtering it. This will allow masking the experimental arm to the study participants.

Preparation of classrooms

Field workers will arrive 30 minutes before the experiment begins to prepare the classrooms. Air purifiers will be installed in classrooms, which will begin to work with empty classrooms. Air purifiers will be running from 30 minutes before the experiment until the end of the 2-hour experimental session. Laptop computers with the tests and questionnaires to be administered will be installed in the classroom (each student will have a laptop). We will install in each of the classrooms the following monitors that will run continuously from 30 minutes before the session until the end of the 2-hour experimental session: a Microaeth (AethLabs, USA) to measure black carbon levels; a DustTrak (TSI, USA) to measure particulate matter with a diameter of less than 2.5 µm ($PM_{2.5}$); and an Extech (USA) to measure levels of CO_2 and values of temperature and humidity.

Participation of students in the classrooms

Each group of students will go to classroom they were assigned at random. In the two classrooms, the same activities will be carried out for a duration of 2 hours, in which the students will have to remain in the classroom.

The chronology of the activities will be the following:

- Assignment of groups to classrooms and initial explanation of the activities (10 minutes).
- Completing the baseline Attention Network Task (ANT, adult version, Flanker task) (15 minutes).
- Completing the PMA-R (Primary Mental Aptitudes) test (10 minutes).
- Watch several videos related to Science and Environment (50 minutes).
- Completing a questionnaire about the videos (5 minutes).
- Completing the post Attention Network Task (10 minutes).
- Completing a questionnaire on factors that can affect attention, designed by the students (10 minutes).
- Completing a short version of the Global Preferences Survey (10 minutes).

The tests and questionnaires will be completed wearing headphones to block the noise.

Description of questionnaires and tests

Attention outcomes are all derived from the Attention Network Task-Flanker Task (ANT). It is a computerized test that takes approximately 9 minutes to complete. A row of five arrows appears either above or below a fixation point. Participants have to use the arrow keys from the keyboard to indicate as quickly as possible if the central arrow is pointing to the left or to the right. They have to ignore the flanker arrows, which point in either the same (congruent) or opposite (incongruent) direction than the middle arrow. The target can be preceded by no cue; a center cue or a double cue, which inform about the upcoming of the target but not on its location; or an orienting cue that alerts about the upcoming of the target as well as its location (orienting cue). The task includes four experimental blocks of 32 trials each (a total of 128 trials) (Forns et al. 2014).

A measure of intelligence is obtained from the PMA-R (Primary Mental Aptitudes - Reasoning) test. This test presents different series of letters, and the user has to guess which should be the next letter of the series by choosing one of the 6 options shown in the screen. The test lasts 6 minutes and the final score is the total number of correct responses.

The variables on decision making with respect to risk, time and social considerations will be obtained from a short version of the Global Preferences Survey (https://www.briq-institute.org/global-preferences/home), a questionnaire on economic preferences (Falk 2016, 2018) . In particular, the blocks administered will include those relating to preferences against risk, time (patience) and social values.

In addition, there will be a citizen science component in which students will propose a set of factors that they believe can influence attention. Specifically, each class will design a 10-item questionnaire with such factors at the beginning of the study. The final questionnaire that will be administered to students during the experiment will be composed of 25 questions selected from the pool of proposed questions. At the end of the study, the items in this questionnaire will be compared with the results of the attention test as a way to validate the students' hypotheses.

Outcome Measures

The following variables will be considered as primary outcome measures:

1. Response speed consistency throughout the Attention Network Task-Flanker Task (post ANT). Calculated as hit reaction time standard error for correct responses (HRT-SE). A higher HRT-SE indicates highly variable reactions related to inattentiveness

2. Combined risk taking score. Risk taking = 0.4729985 × "Risk preference score" + 0.5270015 × "Willingness to take risks", that follows the parameters of Falk et al (2018), where the "Risk preference score" is the final node in the risk tree (see the online appendix of Falk et al (2018)), which is a value between 1 and 32, ranked by the level of risk aversion, and the "Willingness to take risks" refers to the answer to the question on one's willingness to take risks.

3. Combined patience score. Patience = 0.7115185 × "Time preference score" + 0.2884815 × "Self assessment of patience", that follows the parameters of Falk et al (2018), where the "Time preference score" is the final node in the time tree (see the online appendix of Falk et al (2018)), which is a value between 1 and 32, ranked by the level of patience, and the "Self assessment of patience" refers to the answer to the question on the self-assessment of patience (willingness to give up something today).

4. Positive reciprocity score. Positive reciprocity = 0.4847038 × "Willingness to return favor" + 0.5152962 × "Size of gift", that follows the parameters of Falk et al (2018), where "Willingness to return favor" refers to the answer to the question on the willingness to return a favor, and "Size of gift" refers to the answer to the question on the reported size of the gift that would return to a stranger.

5. Altruism score. Altruism = 0.6350048 × "Willingness to give to good causes" + 0.3649952 × "Hypothetical donation", that follows the parameters of Falk et al (2018), where "Willingness to give to good causes" refers to the answer to the question on the willingness to give to good causes, and "Hypothetical donation" refers to the answer to the question on the size of the hypothetical donation one would be willing to make.

6. Trust. Answer to the question "I assume that people have only the best intentions".

The following variables will be considered as secondary outcome measures:

7. Impulsivity (from ANT). Number of incorrect responses (responses made in the opposite direction to the direction of the target arrow).

8. Selective attention (from ANT). Number of omission errors (failure to respond).

9. Alerting score (from ANT). Subtracting the median RT for double cue from median RT for the no cue condition (calculations performed after removing the incongruent trials).

10. Orienting score (from ANT). Subtracting the median RT for spatial cue from the RT for central cue (calculations performed after removing the incongruent trials).

11. Conflict score (executive attention) (from ANT). Participant's median RT for each flanker condition (across cue conditions) and subtracted the congruent from the incongruent RTs.

12. Self assessment of how good they are in math. Answer to the question on how good they are in math.

Data collection

The data that will be collected include the sex of the student, the birth year, the high-school, class, classroom to which the student was assigned (sham or true air purifier), the computer ID in which the task was carried out and the responses to the questionnaires and tests. All the data will be recorded on the computer. No identifying data will be collected, so it will not be possible to link answers to participants, as no names or personal data will be collected.

Statistical power calculation

A previous study (Sunyer et al., 2017) detected a mean reduction of 5 ms in the hit reaction time standard error for correct answers (HRT-SE) calculated from the ANT test, which we will take as our main outcome, associated with a 37% increase in the concentration of NO_2, a marker of exposure to traffic pollution. With the air purifier it is expected to achieve a 80% reduction in the concentration of fine particles, which is why we expect to find a difference of 10 ms in HRT-SE between the group that goes to the purified classroom and the ones that go to the regular classroom. Bearing in mind that the standard deviation of HRT-SE is 90 ms (Sunyer et al., 2017), to have a statistical power of 80% with a type I error of 5% in the comparison of the two groups, it is necessary to include 2,500 students. Assuming a participation of 25 of the 30 children for each participating class, the participation of 100 classes is required. By recruiting high schools with 2 or more lines, it is expected to have to recruit about 35 high schools.

Data analysis

We refer to the Statitical Analysis Plan of the project (Responsible statistician: Xavier Basagaña). Please see separate file.

Ethics

The project obtained Ethical approval from CEIM Parc de Salut Mar (Approval Number: 2018/7968/I). In accordance with the Spanish regulations, our Local Ethics Committee monitors the implementation of the study by approving all the protocols (including the participant's Information Sheet and the Consent Form) of the project. All ISGlobal researchers are regulated by the PRBB Code of Good Practices.
(http://www.prbb.org/system/uploads/attachment/file/3/en/eng_a4.pdf)
The project will be carried out in accordance with international and national legal and ethical standards, including:

- The Nuremberg Code (1946) addressing volunteer consent and next acting;
- The Revised Declaration of Helsinki in its latest version of 2013.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
- Convention on the Rights of the Child (1990);
- The Respect Code focused on socio-economic research (http://www.respectproject.org)

Personal data protection

The appropriate measures will be taken to guarantee the protection and confidentiality of personal data, in accordance with Regulation (EU) 2016/679 on the protection of individuals with regard to the processing of personal data and the free movement of such data. According to the European regulations, the written consent of all the participants in the study will be obtained and the criteria for anonymizing the data will be applied, so that the material obtained in the framework of the project (questionnaires , tests) will be treated anonymously. The name and other personal data that could allow the identification of the participant will never be linked with the data, so personal identification will not be possible.

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