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Abstract: In a study by Law and colleagues recently published in Neuroimage, the authors reported that wearing a surgical mask during an fMRI scan leads to a statistically significant subject-specific change (30%) in the baseline BOLD level in gray matter, although the response to a sensory-motor task was unaffected. An average increase in end-tidal CO$_2$ of 7.4% was found when wearing a mask, despite little support in the literature for major effects of mask wearing on blood gas levels. We comment on these findings, point out a several relevant limitations of the study design and provide alternative interpretations of these data.

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Commentary

Influence of study design on effects of mask wearing on fMRI BOLD contrast and systemic physiology — A comment on Law et al. (2021)

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A B S T R A C T

In a study by Law and colleagues recently published in Neuroimage, the authors reported that wearing a surgical mask during an fMRI scan leads to a statistically significant subject-specific change (30%) in the baseline BOLD level in gray matter, although the response to the sensory-motor task was unaffected. An average increase in end-tidal CO₂ of 7.4% was found when wearing a mask, despite little support in the literature for major effects of mask wearing on blood gas levels. We comment on these findings, point out a several relevant limitations of the study design and provide alternative interpretations of these data.

1. Introduction

Face masks have been mandated widely to combat the community transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although some discussion of their effectiveness (Czyzpiñka et al., 2020; Brooks and Butler, 2021; Bundgaard et al., 2021) as well as possible adverse effects (e.g. dizziness, headaches, fainting) are ongoing, they have been largely established as both safe and effective. Mask wearing has the potential to modify respiratory function, either respiratory mechanics, altering respiratory drive and thus minute ventilation, or via rebreathing. Although any clinically significant effect has been largely discounted, minor changes may be relevant for physiological investigations. The possible impact of mask wearing on cognitive activity such as e.g. neuroscientific studies involving fMRI while subjects are required to wear a mask and on human physiology are also of rising interest. However, only a limited number of studies has been published addressing these important research questions. While in a study in elderly no statistically significant change in arterial oxygenation (SpO₂) after wearing a mask for one hour was found (Chan et al., 2020), another study (Bharatendu et al., 2020) reported that wearing a N95 face mask increases cerebral hemodynamic and end-tidal carbon dioxide pressure (Pₑ₂CO₂). The study of Law et al., published recently in Neuroimage (Law et al., 2021), detected a significant change in gray matter BOLD signal baseline and end-tidal carbon dioxide pressure (Pₑ₂CO₂), but no significant alterations in task-induced BOLD changes due to wearing a mask. We commend Law et al. for performing this important, timely and necessary study investigating possible effects of mask wearing on cerebral hemodynamics and possible influences on evoked brain activity. We would like to highlight several relevant limitations of the study design, and interpretation of their studies data that we feel are instrumental to deliver future research in this area.

2. End-tidal CO₂: not an optimal marker to assess hypercapnia induced by mask wearing

Law et al. employed side stream end-tidal capnography via nasal cannula to measure Pₑ₂CO₂ and approximate the PacO₂. Under ideal conditions with a closed respiratory circuit, e.g. endotracheal intubation, the Pₑ₂CO₂ approximates the alveolar CO₂ and thus PacO₂. This is only partially the case with nasal cannula which are highly positional, sampling expired gases as well as room air in a dynamic fashion (Fukada et al., 1997). In the current investigation an average 7.4% increase in Pₑ₂CO₂ when wearing a mask was reported across subjects (p < 0.0014, paired t-test). There are different interpretations possible for this finding: (i) Reduced sampling of ambient air due to mask wearing, (ii) the occurrence of rebreathing (leading to CO₂ accumulation that is finally inhaled), or (iii) changes in respiration mechanics and respiratory drive finally causing hypercapnia (i.e. changes in respiration rate (RR) and/or tidal volume (VT) can have an effect on Pₑ₂CO₂; the minute ventilation (VT × RR) is inversely related to Pₑ₂CO₂ (Pinna et al., 2006)). That there is an

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Fig. 1. Changes in fMRI BOLD signals and $P_{t Total CO_2}$ as well as $P_{t Partial CO_2}$ during mask-wearing according to the publication of Law et al. (Law et al., 2021) (a-c) and our own measurements (Fischer et al., 2021) (d-g). When comparing the conditions “mask on” and “mask off” no statistically significant difference is present between changes in BOLD task contrast (a) and BOLD baseline shift (b). (c, d, e) Statistically significant increases in $P_{t Total CO_2}$ during mask-wearing were found by Law et al. ((c), from Table 2, measurements inside the scanner) and in our own study: the effect was observed by using two different types of masks, i.e. a FFP2 mask (d) and a surgical mask(e). (f, g) According to our measurement, $P_{t Partial CO_2}$ did not change significantly during wearing a mask (surgical or FFP2) for 10 min, which indicates that $P_{t Total CO_2}$ during mask-wearing provides unreliable data.

It is therefore not straightforward to use $P_{t Total CO_2}$ as a surrogate for arterial $CO_2$ ($P_{a CO_2}$), because it more closely approximates $P_{a CO_2}$ and its sampling is not affected by mask wearing (Stieglitz et al., 2016). We are aware that the measurement of $P_{t Total CO_2}$ inside a running MRI scanner is unusual but successful $P_{t Total CO_2}$ measurements inside a MRI scanner were reported in animal studies (Yamamoto and Kida, 2009; Ramos-Cabrer et al., 2005) and a modification of existing $P_{t Total CO_2}$ probes to be MRI-grade should be possible without too much effort. To underscore the conclusion about the superiority of $P_{t Total CO_2}$ in comparison to $P_{t Partial CO_2}$ in relation to the research question investigated by Law et al., we present results from own measurements (as part of a recent study; Fischer et al., 2021): We measured changes in $P_{t Total CO_2}$ and $P_{t Partial CO_2}$ in adults ($n=13$; median age: 27.0 years) while wearing a mask for 10 min (two types of masks were investigated: a surgical mask and a FFP2 mask; participants sat in a chair and read a scientific text during the experiments which had three phases: 10 min baseline, 10 min mask-wearing, 10 min post-baseline). The data was tested for normality using the Shapiro-Wilk test. Accordingly, we report for normal data mean and standard deviation using a paired T-test as well as for non-normal data median and 95% confidence interval (CI) using a paired Wilcoxon test showing absolute and relative changes. We observed a significant increase in $P_{t Total CO_2}$ (surgical mask: $1.1 \pm 0.7$ mmHg, $2.9 \pm 1.9$ mmHg, $p<0.001$; FFP2 mask: $1.7$ mmHg (95% CI: [1.0, 3.7] mmHg), 4.1% (95% CI: [2.1, 10.5%]), $p=0.001$; $P_{PШру-Вук}=0.025$; Fig. 1(d,e)), but no significant change in $P_{t Partial CO_2}$ (surgical mask: $0.1$ mmHg (95% CI: [−1.7, 0.8] mmHg), 0.4% (95% CI: [−4.4, 2.4%]), $p = 0.845$, $P_{PШру-Вук}=0.033$; FFP2 mask: $0.4 \pm 1.0$ mmHg, $1.3 \pm 2.8$%, $p = 0.154$). Thus, in agreement with the study of Law et al. we also found that wearing a mask increases $P_{t Total CO_2}$, although our increases were smaller: 4.1% for the FFP2 and 2.9% for the surgical mask compared to an increase of 7.4% for Law et al. More importantly, our additional measurements of $P_{t Partial CO_2}$ indicate that the increase in $P_{t Total CO_2}$ is probably due to the improved sampling of end tidal gases retained under the mask, as compared with dilution with ambient air in the un-masked state.

3. The simulation of not mask-wearing by supplying air to the subject via a nasal cannula is prone to cause artefacts

Law et al. noted in some subject an unexpected shift in BOLD baseline signal when air was delivered via the nasal cannula. The authors hypothesized that the sensation of airflow or a change in CO$_2$ from fresh air being introduced in the nose could be the cause. Although this is reasonable, a further option is a change in breathing frequency and depth, which is known to influence PaCO$_2$. Breathing frequency and depth were not measured. Therefore, it is impossible to understand and eliminate the airflow-induced BOLD baseline shift. Importantly, this means that the relationship between mask-wearing and induced BOLD signal changes needs to be interpreted with caution.

4. Possible differences between inside and outside the fMRI scanner need to be taken into account

Law et al. investigated in one subject whether $P_{t Total CO_2}$ was different between inside and outside the fMRI scanner. Indeed, a difference was found (inside: 31.4 mmHg (with mask) and 29.5 mmHg (without mask), compared to outside: 36.0 mmHg (with mask) and 33.7 mmHg (without mask) (Table 2 in their paper). Although the increase in $P_{t Total CO_2}$ from baseline due to mask wearing was similar in both conditions (inside: 6.4%, outside: 6.8%), we wonder how representative this result in one single subject is for the other subjects. In addition, the lower baseline $P_{t Total CO_2}$ inside the scanner in this subject indicates that the $P_{t Total CO_2}$ changes measured for the rest of the group only outside the scanner after the fMRI experiment may not reflect the $P_{t Total CO_2}$ changes happening inside the MRI during the scans. Furthermore, since the $P_{t Total CO_2}$ values measured in the one subject inside the scanner are quite low compared to reference ranges for healthy adults of the same age (e.g. 38 ± 3 mmHg, age: 45 ± 4 years, (Tomoto et al., 2020)), this subject indeed was mildly
hypocapnic. The reason may likely be a stress-induced mild hyperven-
tilation while being in the scanner. This indicates that from a method-
ological point of view, it is necessary to measure the CO₂ parameters, i.e. PTICO₂ and PETO₂, during the fMRI scans. Thus, measurements of changes in fMRI BOLD and CO₂ parameters need to be obtained in parallel when investigating mask-wearing effects.

5. The shift in baseline fMRI bold signal during mask-wearing: a second look at the data

According to Law et al., during the mask-on condition a statistically significant average increase in the baseline BOLD signal of 30.0% was found. However, a reanalysis of the data given in Table 1 shows that the “fractional baseline shift data ΔSf” for the condition “with mask” are not normally distributed (Shapiro-Wilk test, p < 0.01), because one ΔSf value of the population is an extreme value (subject #5, ΔSf = 172.6%). This indicates that the mean is not the correct measure to characterize the central tendency of the distribution; the median needs to be used. Applying the median results in a statistically significant (p = 0.035; Wilcoxon signed-rank test; Shapiro-Wilk test for normality: p = 0.01) median absolute increase of only 8.7% (95% CI: [−2.3, 14.8]%) instead. Another aspect is that also the difference of the individual ΔSf values between the two conditions (with and without mask) is relevant, i.e. Δ(ΔSf). Calculating it gives a mean absolute change of 26.8 ± 74.6% and a Δ(ΔSf) distribution not statistically different from zero (p = 0.379, T-test). Fig. 1(a,b) visualizes the paired data distribution for the BOLD task contrast and baseline shift. Together these two points question the arguments provided by Law et al. that mask-wearing caused an increase in the BOLD signal of 30%.

6. The cerebrovascular CO₂ reactivity reported: a reanalysis of the data

Law et al. determined the BOLD reactivity to ΔPETCO₂ (CVR) to be 0.36%/mmHg. Based on the data provided in Tables 1 and 2 and using the BOLD baseline change differences between the two conditions (mask on, mask off) we obtain a median value of 0.7%/mmHg (95% CI: [−14.6, 118.5] mmHg) (Shapiro-Wilk test for normality: p < 0.01) from their data. This CVR value is relatively high compared to normal reference values, e.g. 0.190%/mmHg (Hou et al., 2020). However, the measurements of Law et al. have a very high scatter, i.e. the CVR value associated with a very high uncertainty. The main problem with the CVR value reported by Law is, however, that CVR should be determined when measuring both brain hemodynamics and PETCO₂ simultaneously.

7. Conclusions and outlook

Law et al. for performed a timely and important study, but with relevant limitations in the study design, which in our opinion require alternative interpretations. For future neuroimaging studies investigating the effect of mask-wearing we recommend to (i) measure changes in PaCO₂ simultaneously with measurements of brain activity and hemodynamics, (ii) employ valid measures of PaCO₂, (iii) test the effect of different types of masks, i.e. cloth, surgical, FFP2 and FFP3, combinations of masks, because this masks have a different breathing resistance, (iv) test how different durations of mask-wearing have an effect on physiology, because there could be habituation effects, (v) evaluate the physiological effects of mask-wearing in populations of different age groups (since the cerebrovascualar reactivity is age-dependent and age could be also associated with stress induced by mask-wearing with subsequent changes in respiration) (vi), employ a set of techniques to measure changes in neuronal activity, cerebrovascular state and systemic physiology (since all may change by mask-wearing), and (vii) ensure that the appropriate statistical analysis and description of the data are used.

References

Bharatendu, C., Ong, J.J.Y., Goh, Y., Tan, B.Y.Q., Chan, A.C.Y., Tang, J.Z.Y., Lew, A.S., Chin, A., Sooi, K.W.X., Tan, Y.L., Hong, C.S., Chin, B.Z., Ng, E., Foong, T.W., Teoh, H.L., Ong, S.T., Lee, P., Khoo, D., Tsivgoulis, G., Alexandrov, A.V., Sharma, V.K., 2020. Powered Air Purifying Respirator (PAPR) restores the N95 face mask induced cerebral hemodynamic alterations among Healthcare Workers during COVID-19 Outbreak. J. Neurol. Sci. 417 (15), 117078.
Brooks, J.T., Butler, J.C., 2021. Effectiveness of mask wearing to control community spread of SARS-CoV-2. JAMA 325 (10), 998–999.
Bundgaard, H., Bundgaard, J.S., Raanshou-Pedersen, D.E.T., et al., 2021. Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-
CoV-2 infection in Danish mask wearers: a randomized controlled trial. Ann. Intern. Med. 174 (3), 325–343.
Chan, N.C., Li, K., Hirsh, J., 2020. Peripheral oxygen saturation in older persons wearing nonmedical face masks in community settings. JAMA 324 (22), 2323–2324.
Czyzonka, T., Greenhalgh, T., Basler, D., Bryant, M.B., 2020. Masks and face coverings for the lay public: a narrative update. Ann. Intern. Med. 172–6625.
Fukuda, K., Ichinohe, T., Kaneko, Y., 1997. Is measurement of end-tidal CO₂ through a nasal cannula reliable? Anesth Prog 44 (1), 23–26.
Fischer, J.B., Kobayashi, L., Scholkman, F., Delgado-Mederos, R., Mayos, M., Durdurian, T., 2021. Cerebral and systemic physiological effects of wearing face masks in young adults. Proc. Natl. Acad. Sci. USA In press.
Geis, O., 2021. Effect of wearing face masks on the carbon dioxide concentration in the breathing zone. Aerosol Air Qual Res 21 (2), 200403.
Hou, et al., 2020. The association between BOLD-based cerebrovascular reactivity (CVR) and end-tidal CO₂ in healthy subjects. Neuroimage 207, 116365.
Law, C.S., Lan, P.S., Glover, G.H., 2021. Effect of wearing a face mask on fMRI bold con-
trait. Neuroimage 229, 117752.
Pinna, G.D., Maestri, M.T., La Rovera, M.T., Gabbi, E., Fanfulla, F. 2006. Effect of paced breathing on ventilatory and cardiovascular variability parameters during short-term investigations of autonomic function. Am. J. Physiol. 290 (1), H424-H433.
Ramos-Cahuber, P., Weber, R., Wiedermann, D., Hoehn, M., 2005. Continuous noninvasive monitoring of transcutaneous blood gases for a stable and persistent BOLD contrast in fMRI studies in the rat. NMR Biomed. 18 (7), 440–446.
Sieglie, S., Matthes, S., Prienrütz, C., Hagmeyer, L., Randerath, W., 2016. Comparison of transcutaneous and capillary measurement of PCO₂ in hypercapnic subjects. Respir. Care 61 (1), 98–105.
Tomato, T., Riley, J., Turner, M., Zhang, R., Tarumi, T., 2020. Cerebral vasomotor reac-
tivity during hypo- and hypercapnia across the adult lifespan. J. Cereb. Blood Flow Metab. 40 (3), 600–610.
Yamamoto, T., Kida, I., 2009. Application of transcutaneous blood carbon dioxide monitor-
ing to the magnetic resonance imaging of rat. J. Med. Eng. Technol. 20 (4–5), 164–168.