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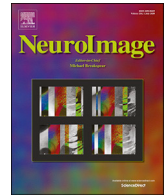
Pichon, Swann; Garibotto, Valentina; Wissmeyer, Michaël; Seimbille, Yann; Antico, Lia; Ratib, Osman; Vuilleumier, Patrik; Haller, Sven; Picard, Fabienne

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# Higher availability of $\alpha 4\beta 2$ nicotinic receptors (nAChRs) in dorsal ACC is linked to more efficient interference control

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## ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are widely distributed in the human brain and play an important role in the neuromodulation of brain networks implicated in attentional processes. Previous work in humans showed that heteromeric  $\alpha 4\beta 2$  nAChRs are abundant in the cingulo-insular network underlying attentional control. It has been proposed that cholinergic neuromodulation by  $\alpha 4\beta 2$  nAChRs is involved in attentional control during demanding tasks, when additional resources are needed to minimize interference from task-irrelevant stimuli and focus on task-relevant stimuli. Here we investigate the link between the availability of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network and behavioral measures of interference control using two versions of the Stroop paradigm, a task known to recruit cingulo-insular areas. We used a previously published PET dataset acquired in 24 non-smoking male subjects in the context of a larger study which investigated the brain distribution of nAChRs in two clinical groups using 2-[(18)F]F-A-85380 PET. We found that higher availability of  $\alpha 4\beta 2$  nAChRs in the dorsal anterior cingulate cortex (ACC) predicted better interference control independently of group and age. In line with animal models, our results support the view that the availability of  $\alpha 4\beta 2$  nAChRs in the dorsal ACC is linked with more efficient attentional control.

## 1. Introduction

Nicotinic acetylcholine receptors (nAChRs) are widely distributed in the human brain and play a major role in the neuromodulation of brain networks important for attention and cognitive functions (Demeter and Sarter, 2013; Levin, 2013; Nees, 2015; Poorthuis et al., 2009; Sarter, 2015). The most abundant high-affinity nAChR in the human brain is the  $\alpha 4\beta 2$  subtype (Albuquerque et al., 2009), which is one of the main subtypes thought to mediate the cognitive effects of nicotine (Changeux, 2010; Valentine and Sofuoglu, 2018).

Previous research in humans has highlighted that stimulation of  $\alpha 4\beta 2$  nAChRs through administration of nicotine, has positive effects on

attention tasks which load on vigilance and alerting (Heishman et al., 2010; Lawrence et al., 2002). Research in rodent models showed that activation of  $\alpha 4\beta 2$  nAChRs in the medial prefrontal cortex enhances performance in sustained attention tasks and evokes abrupt increases in transient cholinergic signals that mediate the detection of task-relevant signals (Demeter and Sarter, 2013; Gritton et al., 2016; Howe et al., 2010; Parikh et al., 2007; Parikh and Sarter, 2008; Young et al., 2013). In addition, it is thought that cholinergic neuromodulation by  $\alpha 4\beta 2$  nAChRs increases tonic cholinergic activity, thereby contributing to the enhancement of attentional control (Demeter and Sarter, 2013). Attentional control is mobilized whenever a demanding situation requires effortful control of selective sensory processing and goal-oriented

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behavior. This is particularly the case when we need to overcome response conflict or errors, when we are confronted to novel situations or have to handle difficult or dangerous situations (Posner and DiGirolamo, 1998). Attentional control has been typically assessed using paradigms where some task-irrelevant information interferes with the task at hand such as in the Stroop paradigm (Stroop, 1935), which requires to overcome interference due to automatic responding to the distracting information. Similar distractor tasks have been used in animal research investigating the role of  $\alpha 4\beta 2$  nAChRs in attentional control (Howe et al., 2010).

In humans, the availability of  $\alpha 4\beta 2$  nAChR receptors across the cerebral cortex was found to be the highest in the anterior cingulate cortex (ACC) and in the anterior insula in non-smoking healthy individuals (Picard et al., 2013). This cortical cingulo-insular network is engaged both during the detection of salient information (Corbetta and Shulman, 2002; Seeley et al., 2007), and during tasks requiring attentional and executive control (Botvinick et al., 1999; Nee et al., 2007; Posner and DiGirolamo, 1998; Shenhav et al., 2016). These areas are thought to be critically involved in the detection of response conflict and in the monitoring of task performance. The goal of the current study was therefore to investigate whether the availability of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network of human participants may be associated with higher levels of attentional control in tasks which require to focus attention on task-relevant information while overcoming distractor interference. This was achieved by using two versions of the Stroop task (Stroop, 1935), a paradigm known to activate these brain areas (Cieslik et al., 2015).

Cognitive interference arises whenever task-irrelevant information impedes the processing of, and the response to, a task-relevant stimulus, necessitating additional effortful attentional control to adapt performance accordingly and prioritize task-relevant information. The inhibitory control of attention enables us to selectively attend to the relevant stimulus dimension for the task at hand, while suppressing the attention that we may pay to task-irrelevant information (Diamond, 2013; Posner and DiGirolamo, 1998). As participants experience interference, they must deploy more attentional control to answer correctly. In the lab, interference control is often measured using the Stroop paradigm, one of the most robust paradigm used to measure control in the face of interference and one of the most well-studied cognitive phenomena in psychology (MacLeod, 1991; Stroop, 1935). In the standard color version of the Stroop task, participants have to name the ink color of a word that spells a color name. When the ink and the word are congruent (e.g., the word “green” in green letters, called non-interference or congruent trials), the task is simple and no interference occurs. However, when the ink and the word do not match (e.g., the word “green” in red letters, called interference or incongruent trials), participants experience an interference between both dimensions, they commit more errors and reaction times (RTs) augment. Stroop interference is therefore indexed by a slowing down of RTs during incongruent trials compared to congruent trials. Inter-individual differences in Stroop interference have been interpreted as reflecting differences in attentional control efficacy, and individuals with lower attentional control are expected to display a greater slowing down of RTs during incongruent trials due to their difficulty in coping with interference (Kiefer et al., 2005; Long and Prat, 2002).

Previous fMRI studies which investigated interference control have repeatedly found activation in a cortical network comprising the dorsal ACC and the anterior insular cortex, which is recruited when participants overcome cognitive interference (Barch et al., 2000; Botvinick et al., 1999; Braver et al., 2001; MacDonald et al., 2000; Nee et al., 2007; Pardo et al., 1990; Sohn et al., 2007). A prominent model (Botvinick, 2007; Botvinick et al., 2001) proposed that the dorsal ACC signals the occurrence of conflict and serves as an index for the demand and the monitoring of control, while the adjustment of behavior is implemented by the dorsolateral prefrontal cortex (dlPFC; Boschini et al., 2017; MacDonald et al., 2000). The monitoring of conflict in the dorsal ACC is therefore

thought to provide a signal to attentional control mechanisms. The role of the anterior insula in cognitive interference is less clear. It is generally co-activated with the dorsal ACC during cognitive interference, as well as in various cognitive, affective, and regulatory functions, and is believed to be part of a saliency network which assists target brain regions in the generation of appropriate behavioral responses to salient stimuli (Corbetta and Shulman, 2002; Menon and Uddin, 2010). Notably, throughout the cortex, the cingulo-insular network displays the highest availability of  $\alpha 4\beta 2$  nAChRs in non-smoking healthy individuals (Picard et al., 2013), potentially suggesting an implication of dorsal anterior cingulate and anterior insular  $\alpha 4\beta 2$  nAChRs signaling in interference control.

Here our goal was to characterize this relationship at the inter-individual level using a brain-behavior correlational approach with PET imaging. We hypothesized that higher availability of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network, should favor attentional control, and therefore predict a higher efficiency in resolving cognitive interference, as indicated by lower levels of interference costs measured using two variants of the Stroop paradigm. The *in vivo* cerebral distribution and availability of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network important for interference control was assessed in 24 subjects who were part of a study which used 2-[(18)F]F-A-85380 (F-A-85380) PET (Garibotto et al., 2019). Immediately after the PET exam, we administered a color version and a numerical version of the Stroop task to estimate participants' efficiency in resolving cognitive interference.

## 2. Materials and methods

**Experimental procedure and behavioral tests:** Upon arrival to the hospital, all participants underwent a PET exam using F-A-85380 - a specific tracer of the nAChR  $\beta 2$  subunit - and a 3D T1 MRI (Garibotto et al., 2019). Immediately after the PET exam, subjects underwent behavioral testing. They completed a standard Stroop color test and a numerical version of the Stroop test. The order of tests was randomized across participants.

**Participants:** We recruited 24 non-smoking male subjects in the context of a larger study which aimed at investigating the brain distribution of nAChRs in different clinical groups, including a group of individuals with idiopathic generalized epilepsy and a group of control subjects (Garibotto et al., 2019). Twelve participants were diagnosed with adolescence-adult onset idiopathic (or genetic) generalized epilepsy (IGE group, mean age  $\pm$  SD:  $34.1 \pm 8.7$  years; range: 18–51) and twelve participants were healthy age-matched volunteers (control group, age  $34.2 \pm 9.9$ , range: 18–51). Both clinical groups were pooled in our final analysis to reach reasonable power. We carefully ensured that there was no significant group difference in our cognitive and brain measures of interest. Furthermore, we ensured that no residual variance may be accounted by confounding factors like group or age, by regressing out the effect of group and age from all behavioral and neural variables used in the regressions of interest. Finally, we also included in all figures the distributions and the regression slopes for each clinical group to ensure they were comparable (see the statistical analyses section below).

We excluded subjects with a diagnosis of neurological disorders other than epilepsy or psychiatric disorders, sleep disorders, brain lesions on MRI, cardiac disorders, asthma, renal or hepatic failure, hyperthyroidism, type 1 diabetes or severe dyslipidemia. The consumption of tobacco or of any drug of abuse during the last twelve months was also an exclusion criterion. Importantly, none of the epileptic patients included reported any seizure occurring within the week before the F-A-85380-PET.

All procedures performed in this study were in accordance with the Swiss ethical standards and with the 1964 Helsinki declaration and its later amendments. The study protocol was approved by the Ethics Committee of the Geneva University Hospitals (CER 10-041) and by the Swiss agency for medications (Swissmedic: study n°2011DR1031). Written informed consent was obtained from all participants.

**The color Stroop task:** We used a standard Stroop task to estimate

inter-individual differences in interference control (Stroop, 1935). In each trial, subjects were presented the words (Red, Blue, Yellow or the neutral string “XXXX”) printed in Red, Blue or Yellow colors. Subjects’ task was to report the color in which the word was printed. As reading is more automatic than reporting colors, trials where the color and the semantic content of the word are incongruent cause an interference and provoke slower reaction times (RTs) than for trials where both dimensions are congruent. Participants performed 160 trials. Trials pertained to three experimental conditions, corresponding to whether or not the semantic and color dimensions of the words were congruent (i.e. the word “RED” printed in RED, 41% of trials) or incongruent (i.e. the word “BLUE” printed in RED, 50% of trials). A third condition called neutral used the non-semantic string “XXXX”, which provokes no interference (9% of trials). Stimuli were presented during 250 ms and subjects were given 2 s to answer. The frequency of transitions between congruent and incongruent trials was equated.

**The numerical Stroop task** is one multiple variant of the classical Stroop test. In each trial, participants are presented with a string composed of 1–4 repetitions of the same digit that could be either 1, 2, 3, 4 or the character “X” (i.e. string such as “3”, “44”, “333” or “4444”). Participants’ task was to report the number of symbols appearing on the screen, while ignoring the meaning of the repeated digit. Since number reading is more automatic than reporting the number of digits, trials in which the number of digit and the specific digit used are incongruent cause an interference and induce slower RTs than trials in which both dimensions are congruent. Participants performed 160 trials, which pertained to three experimental conditions corresponding to whether or not the numeric value and the number of digits of the stimulus were congruent (i.e. the string “333” or “4444”, 41% of trials), incongruent (i.e. the string “2” or “444”, 50% of trials), or neutral (when the non-interfering symbol X was used, 9% of trials). Stimuli were presented during 250 ms and subjects were given 2 s to answer. The frequency of transitions between congruent and incongruent trials was equated. Note that due to a programming bug detected in the early stage of the experiment, the first 5 subjects received a higher proportion of incongruent trials (78%), which did not hinder the estimation of the interference score.

**Stroop interference score:** To quantify cognitive interference, we used a ratio score between the average RT for incongruent trials and for congruent trials. Computing the ratio rather than the difference has several computational advantages, including the fact that the interference score estimated using a ratio is more comparable between subjects than a difference score, since it is normalized for subjects’ processing speed (Lansbergen et al., 2007). The higher the interference score, the lower the ability of the participant to handle cognitive interference.

**Statistical analyses used for behavioral tests:** We used repeated measures ANOVA with a within factor condition (congruent, incongruent, neutral) to analyze average accuracy scores and average RTs in each Stroop tasks. Accuracy scores were estimated without taking into account occasional missing responses. RTs were estimated on correct trials. Subjects with accuracy scores below 80% were not considered in the analysis. One-tailed t-tests were used to assess differences between incongruent and congruent/neutral conditions, anticipating that incongruent trials would generate more errors and be slower than congruent or neutral trials. Effect size were computed using Cohen’s d for paired samples.

Despite the absence of group difference in our measures of interest, we protected against any possible trend of the group and age factors by removing their effect from binding potential values ( $BP_{RI}$ ) and interference score values before running the main correlation of interest, corrected for group and age. We used standard regressions with  $BP_{RI}$  and interference score values as dependent variables, and age and group as independent variables. The residuals of these regressions were used as final  $BP_{RI}$  values and interference scores uncontaminated by age and group in standard regressions and correlations. Note that, to allow a more simple visual interpretation of the regressions, the constant value of the

intercept was added back to the residuals to keep the unit of each measure intact and avoid zero centering. Note that adding a constant to the residuals has no impact on the value of the correlation coefficient or of the statistics. Shapiro normality tests were performed on the variables used in the final correlations and parametric or non-parametric correlations were used accordingly. We used 1-tailed correlation tests as our hypothesis anticipated a negative relationship between  $BP_{RI}$  values and Stroop interference scores.

**Imaging data acquisition and preprocessing:** The following methods have been already described in a previous study (Garibotto et al., 2019). 3D T1 MPRAGE images were acquired with a 3T Siemens Prisma MRI scanner (Erlangen, Germany) in sagittal orientation, 176 slices, voxel size  $1 \times 1 \times 1$  mm<sup>3</sup>, TE 1.94 ms, TR 2300 ms, 1 average. PET images were acquired 180 min after injection of 200 MBq (mean  $\pm$  SD:  $202 \pm 9$  MBq, range: 187–217) of F-A-85380, using a Siemens Biograph PET/CT tomograph, with a simplified static 60 min acquisition protocol, previously validated against full quantification (Gallezot et al., 2005; Picard et al., 2006). In order to minimize differences in the activation state of the cholinergic system, all subjects were kept in a comparable resting awake condition between the injection and the PET acquisition, which started 3 h later and lasted 1 h.

In brief, we calculated volume of distribution ( $V_t$ ) parametric images at 210–240 min post injection with respect to the free fraction of unmetabolized F-A-85380, as measured in venous blood during the acquisition. We subsequently calculated parametric images of the specific uptake ratio of different brain regions with respect to the corpus callosum, coined “ratio index of binding potential ( $BP_{RI}$ )” and computed with the established formula:  $[BP_{RI} \text{ voxel} = (V_t \text{ voxel} / V_t \text{ corpus callosum}) - 1]$  (Garibotto et al., 2019; Okada et al., 2013).  $BP_{RI}$  measures the density of “available” receptors, and is a composite measure which depends on receptor density and affinity. PET images were processed using the SPM12 software (Penny et al., 2007). PET images were coregistered to individual T1 MR images, spatially normalized to the standard Montreal Neurological Institute (MNI) space using the deformation matrix derived from the normalization of the T1 MR image, and spatially smoothed with an isotropic 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

**Region of interest (ROI) analysis:** Given the targeted network, we used the [Neurosynth.org](http://Neurosynth.org) database - which allows for robust and large-scale synthesis of neuroimaging studies (Yarkoni et al., 2011) - to identify the cingulo-insular network involved in resolving cognitive interference in Stroop studies (Nee et al., 2007). We performed a meta-analysis of brain-imaging studies using the term “Stroop”, which yielded a large corpus of 225 studies. Based on this corpus, Neurosynth generates two statistical maps: an association map and a uniformity map (Yarkoni et al., 2011). The association map displays the false discovery rate (FDR) corrected probability that a voxel is *specifically* activated in Stroop studies compared to other studies. The uniformity map, which overlaps with the association map, displays the FDR corrected probability that a voxel is *consistently*, but not specifically, activated during the resolution of cognitive interference in Stroop studies. In the association map, the cluster with the highest probability of being selectively reported in previous Stroop studies was located in the dorsal ACC at the MNI coordinate xyz = [8; 22; 38]. In the uniformity map, the anterior insula was found constantly, but not specifically, activated bilaterally in the large corpus of Stroop studies, at MNI coordinates [xyz = 36/22/0 and -32/22/2]. This highlights the fact that the anterior insula shows a wide range of activation patterns in cognitive and affective tasks that are not specific to Stroop studies (Chang et al., 2012; Nee et al., 2007). The two anterior insula clusters highlighted by Neurosynth (left: 555 voxels, right: 877 voxels) were pooled in a single anterior insula mask given we had no laterality hypothesis (and indeed no effect of laterality was observed in *post-hoc* tests). Both the dorsal ACC cluster (90 voxels) and the anterior insula clusters were used as ROI masks for extracting  $BP_{RI}$  values. Finally, even though previous data in humans point to a higher expression of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network (Picard et al.,



2013) compared to other cortical regions, we extracted  $BP_{RI}$  values from a dlPFC ROI since the dlPFC is also engaged by Stroop interferences as highlighted by the Neurosynth uniformity map. Given the considerable spatial extent of the dlPFC clusters, which included other prefrontal regions, we used a spherical ROI centered at MNI coordinates [xyz = 44/10/32 and -44/22/2] with 6 mm radius (each ROI was 123 voxels). The dlPFC ROIs were pooled in a single dlPFC ROI given that we had no laterality hypothesis (and indeed no effect of laterality was observed).  $BP_{RI}$  values were averaged across voxels in each ROI for each subject.

Finally, we also computed a ROI analysis (Fig. 1B) to investigate whether mean  $BP_{RI}$  values were higher in the cingulo-insular ROIs, than mean  $BP_{RI}$  values in the dlPFC ROI or in other cortical regions as previously shown in (Garibotto et al., 2019; Picard et al., 2013). For the cingulo-insular ROI, we used the ROIs described above. For the ROI including all other cortical regions than the cingulo-insular ROI described above, we included all cortical regions from the AAL Atlas (Tzourio-Mazoyer et al., 2002), excluding the AAL cingulate areas and the AAL insular cortex. For each subject and each ROI, a single mean value was obtained by averaging  $BP_{RI}$  values across all the voxels in the ROI.

### 3. Results

**Color Stroop task:** One participant performed abnormally low (74% correct responses for the global performance, including 66% correct responses for neutral trials) and was excluded from further analyses in this task. The average accuracy of remaining participants was excellent (mean  $\pm$  SD = 95.7%  $\pm$  3.4) and comparable between conditions ( $F(2,44) = 3.11$ ,  $p = 0.054$ ,  $\eta_p^2 = 0.07$ ). It reached 94.4%  $\pm$  4.9 for incongruent trials, 97%  $\pm$  3.8 for congruent trials, and 97.3%  $\pm$  5.5 for neutral trials. Incongruent trials generated more errors than congruent trials ( $t(22) = 2.34$ ,  $p = 0.028$ ,  $d = 0.49$ ) but not more errors than neutral trials ( $t(22) = 1.8$ ,  $p = 0.08$ ,  $d = 0.38$ ).

Average RTs for correct trials differed between conditions ( $F(2,44) = 29.16$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.092$ ). As expected, RTs for incongruent trials (773 ms  $\pm$  158) were slower than for congruent (665 ms  $\pm$  127,  $t(22) = 8.3$ ,  $p < 0.001$ ,  $d = 1.74$ , see Fig. 1) and for neutral trials (691 ms  $\pm$  157,  $t(22) = 5$ ,  $p < 0.001$ ,  $d = 1.05$ ).

Importantly, the IGE group did not differ from the group of control subjects in accuracy ( $p = 0.98$ ), in global reaction times ( $p = 0.78$ ) or in interference ratio scores ( $p = 0.56$ ).

**Numerical Stroop task:** One participant performed abnormally low (72.4% correct responses) and was excluded from further analyses. The average accuracy was excellent (96.8%) but differed between conditions ( $F(2,44) = 9.79$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.16$ ). It reached (mean  $\pm$  SD) 95.5%  $\pm$  3.7 for incongruent trials, 98.3%  $\pm$  2.8 for congruent trials and 98.4%  $\pm$  3.4 for neutral trials. Incongruent trials generated more errors than

congruent trials ( $t(22) = 4.21$ ,  $p < 0.001$ ,  $d = 0.88$ ) and than neutral trials ( $t(22) = 3.51$ ,  $p < 0.002$ ,  $d = 0.73$ ).

Average RTs for correct trials also differed between conditions ( $F(2,44) = 24.9$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.04$ ). As expected, RTs for incongruent trials (705 ms  $\pm$  152) were slower than for congruent trials (651 ms  $\pm$  160,  $t(22) = 7.2$ ,  $p < 0.001$ ,  $d = 1.5$ , see Fig. 1), but not slower than for neutral trials (719 ms  $\pm$  174,  $t(22) = 1.5$ ,  $p = 0.14$ ,  $d = 0.32$ ).

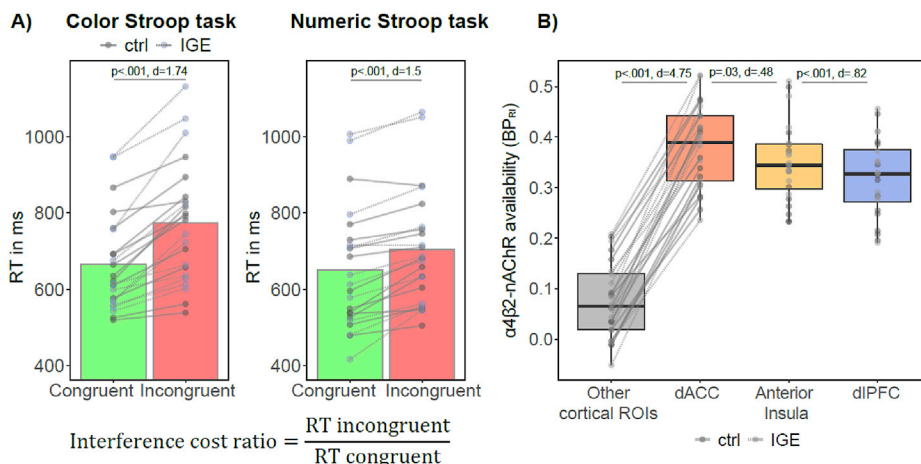
Importantly, the IGE group did not differ from the control group in accuracy ( $p = 0.87$ ), global reaction times ( $p = 0.36$ ), or interference ratio scores ( $p = 0.61$ ).

**ROI analysis:** There was no significant group difference in  $BP_{RI}$  values in the dorsal ACC ROI (mean  $\pm$  SD IGE group: 0.39  $\pm$  0.09, control group: 0.36  $\pm$  0.08,  $t(22) = 0.98$ ,  $p = 0.33$ ) nor in the anterior insula ROI (IGE group: 0.37  $\pm$  0.06, control group: 0.32  $\pm$  0.08,  $t(22) = 1.63$ ,  $p = 0.12$ ) before regressing out the effect of age and group from  $BP_{RI}$  values. We note that this result may seem to contrast with a previous study with the same cohort, which found higher levels of  $BP_{RI}$  values in the IGE group in another region of the ACC (Garibotto et al., 2019), adjacent to the dorsal ACC ROI used here.

The analysis of the cortical distribution of nAChRs indicated that the mean  $BP_{RI}$  value in the cingulo-insular network of interest (averaged across ROIs), was significantly higher (mean  $\pm$  SD: 0.36  $\pm$  0.07) than the mean  $BP_{RI}$  value in all other cortical regions (0.07  $\pm$  0.07,  $t(23) = 35.1$ ,  $p < 0.001$ ,  $d = 7.16$ ), as previously found in (Picard et al., 2013), and in a larger cohort which included the subpopulation of the present study (Garibotto et al., 2019).  $BP_{RI}$  values in the dorsal ACC ROI ( $t(23) = 23.26$ ,  $p < 0.001$ ,  $d = 4.75$ ) and in bilateral insula ( $t(23) = 40.1$ ,  $p < 0.001$ ,  $d = 8.18$ ) were higher than  $BP_{RI}$  values from the ROI including all other cortical regions.  $BP_{RI}$  values in the dorsal ACC ROI (mean  $\pm$  SD: 0.38  $\pm$  0.08) were higher than mean  $BP_{RI}$  values in the anterior insula ROI (0.35  $\pm$  0.07,  $t(23) = 2.36$ ,  $p = 0.027$ ,  $d = 0.48$ , see Fig. 1B).  $BP_{RI}$  values in the dorsal ACC ROI ( $t(23) = 4.96$ ,  $p < 0.001$ ,  $d = 1.01$ ) and in bilateral insula ( $t(23) = 4.05$ ,  $p < 0.001$ ,  $d = 0.82$ ) were also higher than  $BP_{RI}$  values in the bilateral dlPFC ROI (0.32  $\pm$  0.08).

Our goal was to characterize the extent to which inter-individual differences in the availability of  $\alpha 4\beta 2$  nAChRs in the cingulo-insular network found active in Stroop studies, would predict a better efficiency in resolving cognitive interference, independently of age and group. As explained in the Methods section, we regressed out age and group from  $BP_{RI}$  values and from behavioral scores prior to computing the correlations of interest. We used 1-tailed correlation tests as we anticipated a negative link between  $BP_{RI}$  values and Stroop interference scores.

In the dorsal ACC ROI (see Fig. 2), correlation analyses indicated that higher levels of F-A-85380  $BP_{RI}$  predicted lower levels of Stroop interference in the color Stroop task ( $r = -0.41$ ,  $p = 0.025$ ). Despite the low power, we computed correlations for each clinical group. In the color



**Fig. 1. Behavioral results and nicotinic receptor availability in the cingulo-insular network** A) Bar plots showing that mean RTs in both Stroop tasks were slower for incongruent trials than for congruent trials. B) Box plots showing that  $BP_{RI}$  values in the regions of the cingulo-insular network of interest were higher than median  $BP_{RI}$  values in the “other cortical regions” ROI, and than median  $BP_{RI}$  values in the dlPFC. The plain and dotted lines connect averages from the same individuals within each group. Note that distributions were comparable between groups.  $BP_{RI}$  = ratio index of binding potential. ROI = region of interest; dACC = dorsal ACC; dlPFC = dorsolateral prefrontal cortex.

Stroop task, this relationship was significant in the patient group only (healthy group:  $r = -0.32$ ,  $p = 0.16$ ; patient group:  $r = -0.53$ ,  $p = 0.048$ ). For the numeric Stroop task, a correlation computed across all subjects indicated that higher levels of F-A-85380 BP<sub>RI</sub> in the dorsal ACC predicted lower levels of Stroop interference ( $r = -0.55$ ,  $p = 0.0035$ ). Correlations in each clinical group indicated that this relationship was significant in the healthy group only (healthy group:  $r = -0.62$ ,  $p = 0.015$ ; patient group:  $r = -0.49$ ,  $p = 0.06$ ). Note that the lack of significance in the latter tests may reflect the limited power at  $n = 12$ . Since a Shapiro test indicated that the distribution of interference scores in the numerical task was slightly right-skewed ( $W = 0.87$ ,  $p = 0.01$ , all 24 subjects), we also computed a rank correlation (Kendall test) which indicated a non-significant trend toward negative correlation ( $\tau = -0.23$ ,  $p = 0.07$ ) between dorsal ACC BP<sub>RI</sub> values and Stroop interference scores.

In the bilateral insula ROI, we observed no significant correlation between BP<sub>RI</sub> values and interference scores in the color task ( $r = -0.2$ ,  $p = 0.35$ ), nor in the numeric task ( $\tau = -0.08$ ,  $p = 0.3$ ).

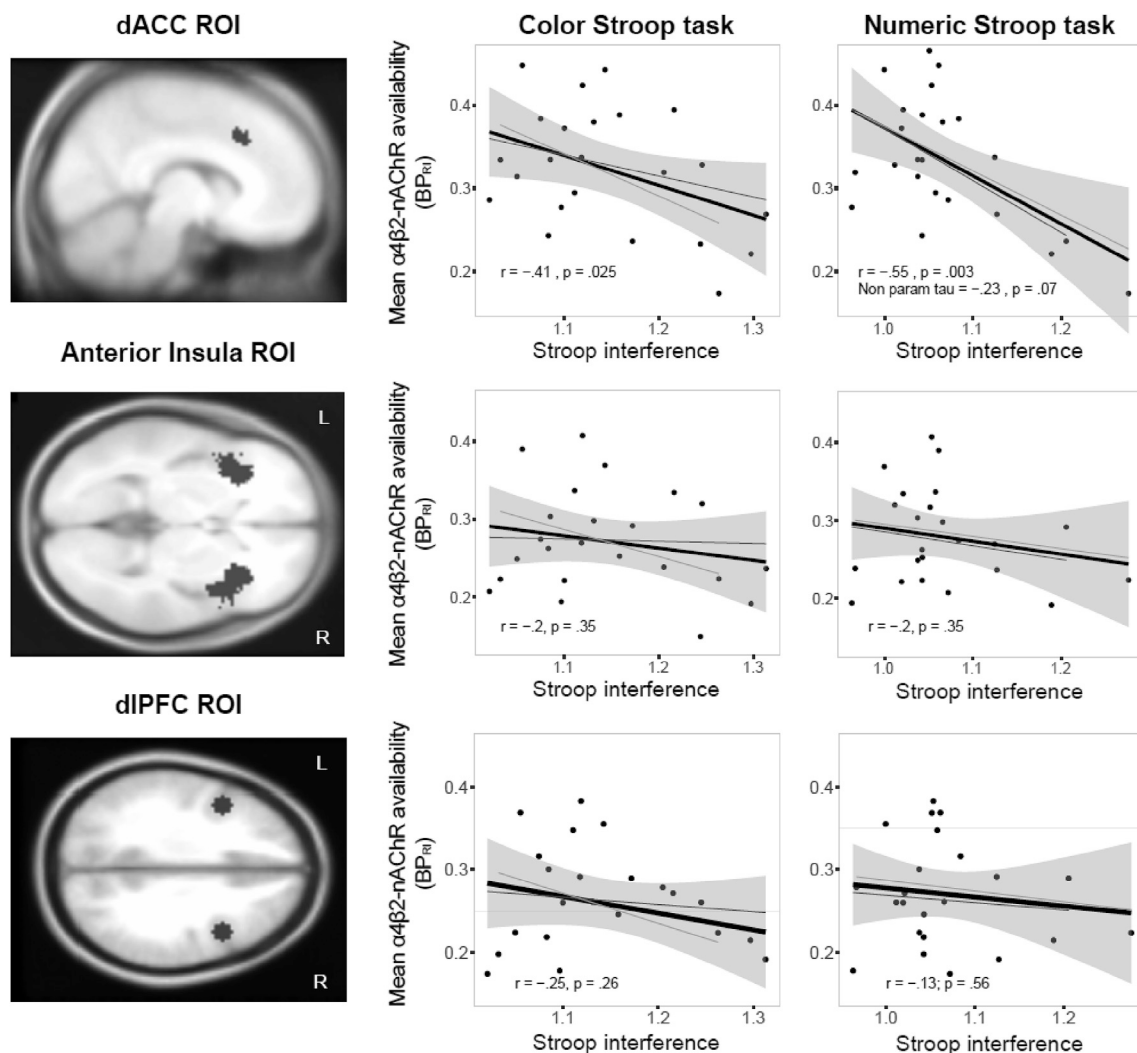
Because the dlPFC was another important cluster identified in the Neurosynth uniformity map for Stroop studies (despite it contains less nAChRs than the dorsal ACC and than the anterior insula), we also

computed post hoc correlations between the extracted BP<sub>RI</sub> values from the dlPFC ROI and the interference scores in either task. We observed no significant correlation in the color Stroop task ( $r = -0.25$ ,  $p = 0.26$ ), nor in the numerical Stroop task ( $r = -0.13$ ,  $p = 0.56$ ).

In the ROI including all the other cortical regions, we observed no significant correlation between BP<sub>RI</sub> values and interference scores in the color task ( $r = -0.21$ ,  $p = 0.16$ ), nor in the numeric task ( $\tau = -0.07$ ,  $p = 0.34$ ).

#### 4. Discussion

Our results show that higher levels of  $\alpha 4\beta 2$  nAChR availability in the dorsal ACC predicted lower levels of interference cost, i.e. higher levels of interference control. A higher BP<sub>RI</sub> value could indicate an increase in receptor density (Picard et al., 2006). It could also reflect a higher rate of high-affinity nAChR subtypes (Moroni and Bermudez, 2006). In either case, this is consistent with the hypothesis that activation of  $\alpha 4\beta 2$  nAChRs may contribute to the recruitment of additional attentional resources when task demands are high (Demeter and Sarter, 2013; Sarter, 2015). Interestingly, despite the fact that the anterior insula, the dlPFC and the dorsal ACC are part of the same network involved in interference



**Fig. 2.** Higher levels of  $\alpha 4\beta 2$  nAChR availability in the dorsal ACC ROI predicted lower levels of Stroop interference in the color version of the Stroop task, which is indicative of more efficient interference control (scatter plots of residualized data after removing the effect of age and group from BP<sub>RI</sub> and Stroop interference values, see methods). This negative correlation was not significant in the anterior insula ROI nor in the dlPFC ROI. The thick regression lines were estimated using all subjects. Dark (healthy) and light (patients) thin regression lines were estimated for each clinical group and showed a net overlap, indicating that this negative relationship was comparable across groups.

control, we did not observe any relationship between  $\alpha 4\beta 2$  nAChR availability and cognitive interference in the anterior insula nor in the dlPFC. Given the hypothesized implication of the insula in saliency processing (Corbetta and Shulman, 2002; Seeley et al., 2007), it does not exclude the possibility that  $\alpha 4\beta 2$  nAChR activation in the anterior insula may support the detection of salient stimuli, an hypothesis which was not tested by the present design and will require further testing.

At a functional level, the computational functions of the ACC, which is at the crossroads between the reward and the motor system, are multiple (Kolling et al., 2016). It has been shown for long that Stroop interference increases activity in the dorsal ACC and in the anterior insula (Barch et al., 2001; Carter et al., 1995; Leung et al., 2000; Pardo et al., 1990). Earlier models have emphasized the role of the dorsal ACC in signaling response-conflict (Botvinick et al., 2001), or in providing an estimate of the likelihood that an error may arise in a given context (Brown and Braver, 2005). For instance, the dorsal ACC - together with the anterior insula - is activated when subjects make errors (Carter et al., 1998; Dehaene et al., 1994; Dosenbach et al., 2006), or when they receive negative feedback following an inappropriate behavioral response (Dehaene et al., 1994; Gehring and Willoughby, 2002). Cingulotomy of the dorsal ACC increases errors and reduces the ability to adapt behavior following negative feedback (Williams et al., 2004). More recent frameworks have extended these earlier views by highlighting the role of the ACC in tracking the value of potential outcomes and in integrating different aspects of decision-making linked to action selection and control (Holroyd and Yeung, 2012; Rushworth et al., 2012, 2004; Shenhav et al., 2016).

On the other hand, the anterior insula is classically identified as an interoceptive region involved in various cognitive and emotional processes (Craig, 2004; Critchley et al., 2004; Singer et al., 2009). More recent accounts have highlighted its frequent recruitment in tasks requiring attention (Corbetta and Shulman, 2002; Menon and Uddin, 2010). The fact that we observed no correlation between the interference score and the availability of  $\alpha 4\beta 2$  nAChRs in the anterior insula should not strictly be interpreted as a dissociation between the function of the two regions, since the signs of the relationships in both regions were negative. Anatomical and resting state studies indicate that the anterior insula is anatomically and functionally connected to the dorsal ACC (Nieuwenhuis, 2012; Taylor et al., 2009). However, these two interconnected regions are not equivalent in their respective patterns of connectivity since the anterior insula shares connections with sensory networks whereas the dorsal ACC shares more connections with the motor system (Craig, 2009). It has been suggested (e.g. Menon and Uddin, 2010) that the core function of the anterior insula is to signal salient events in order to trigger additional processing and initiate, together with the dorsal ACC and other prefrontal regions, adaptive behavioral responses and efficient control of task goal contingencies. The role of the dorsal ACC during cognitive interference may be to allocate additional attentional control and provide information to downstream prefrontal regions responsible for adapting behavior, while the role of the anterior insula may instead be to increase attentional processing of sensory stimuli and to signal interference (Menon and Uddin, 2010; Shenhav et al., 2017).

Some behavioral studies have found that nicotine administration improved interference resolution as measured by a reduction of the Stroop interference effect – or of other conflict-interference effect as in the Posner task (Barr et al., 2008; Meinke et al., 2006; Potter and Newhouse, 2004; Wignall and de Wit, 2011), even though some studies have not observed beneficial effects with similar doses of nicotine (Ettinger et al., 2017; Mancuso et al., 1999; Poltavski and Petros, 2006). Functional MRI studies in humans have shown that nicotine administration increases BOLD activation in the ACC and in fronto-parietal regions when demands on attention are high (Ernst et al., 2001; Lawrence et al., 2002; Thiel et al., 2005).

Work in animal models indicates that cholinergic activation through  $\alpha 4\beta 2$  nAChRs is an important pathway supporting attentional control

(Demeter and Sarter, 2013; Sarter, 2015). Cholinergic neurons from the basal forebrain project to the entire cortex. It is assumed that two types of cholinergic activity contribute to the control of attention (Sarter, 2015). On the one hand, it has been shown that fast transient bursts of cholinergic activity in the medial prefrontal cortex enable the detection of rewarded cues in sustained attention tasks (Parikh et al., 2007). The neuromodulation of this phasic cholinergic activity by  $\alpha 4\beta 2$  nAChRs was shown to increase the production of cholinergic transients and task performance (Howe et al., 2010; Parikh et al., 2008). On the other hand, it has been proposed that the cholinergic system operates via another more sustained tonic component of acetylcholine (ACh) release, which is presumed to be influenced by  $\alpha 4\beta 2$  nAChR activation and which could mediate top-down attentional control and cognitive effort (Demeter and Sarter, 2013; Sarter, 2015; Sarter et al., 2006). Tonic prefrontal cholinergic activity is indeed particularly high in sustained attention tasks that include distractors and require to parse task-relevant from task-irrelevant stimuli (St. Peters et al., 2011). Individual differences in cholinergic neurotransmission have also been associated with differences in attentional control. For instance, rats exhibiting poor attentional control as a trait display reduced cholinergic neurotransmission in the medial prefrontal cortex during a sustained attention task (Paolone et al., 2013). Moreover stimulation of  $\alpha 4\beta 2$  nAChRs through the systemic administration of a partial nAChR agonist improves their attentional performance (Paolone et al., 2013). Our findings seem therefore consistent with those in animal models, and suggest that individual differences in the availability of  $\alpha 4\beta 2$  nAChRs in the dorsal ACC in humans, influence the efficiency of interference control.

Finally, nAChRs are also known to interact, through neuromodulation, with other neurotransmitter systems during tasks requiring attention. Nicotine is known to increase the cortical and subcortical release of acetylcholine, noradrenaline, dopamine as well as serotonin, glutamate and glycine through an action at pre- and post-synaptic nAChRs (Hahn, 2015; Hernandez-Lopez et al., 2013). Noradrenergic transmission has been proposed to contribute to the attention-enhancing effect of nicotine on response speed and stimulus detection (Hahn and Stolerman, 2005). NACHRs are also widely expressed in midbrain dopamine neurons that project to dorsal striatum, nucleus accumbens and prefrontal cortex (Livingstone and Wonnacott, 2009). They may thus modulate the functions associated with these pathways, including attentional control and other executive functions. Interestingly, genetic variations in genes coding for the nAChR  $\alpha 4$  subunit (*CHRNA4*) and for the dopaminergic receptor type D2 (*DRD2*) have been shown to modulate synergistically nicotine effects on distractor interference in a visual search task (Ahrens et al., 2015). Breckel et al. (2015) confirmed that response to nicotinic challenge in a visuospatial attention task depends on polymorphisms in these genes.

Some limitations of our study include the combination of both clinical groups to reach reasonable power. This choice is explained by the problematic exposure of additional control subjects to a radioactive tracer. To limit this problem, we carefully corrected all studied variables for potential residual trends due to age and group, and highlighted a link between inter-individual differences in the availability of  $\alpha 4\beta 2$  nAChRs in the dorsal ACC and interference control independently of age and group. Considering the constraints with radio-exposure, a sample size of 24 is reasonably high, especially with a rarely used tracer, and thus makes the current dataset interesting and valuable. It would nevertheless be important to replicate and extend these findings in a larger sample of healthy individuals.

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## Data availability

The data used for the analyses is available at the following link: <https://osf.io/s72fc/>

## Declaration of competing interest

All authors declare that they have no conflict of interest.

## CRediT authorship contribution statement

**Swann Pichon:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Supervision. **Valentina Garibotto:** Methodology, Formal analysis, Writing - review & editing. **Michael Wissmeyer:** Conceptualization, Methodology. **Yann Seimille:** Resources. **Lia Antico:** Investigation. **Osman Ratib:** Resources. **Patrik Vuilleumier:** Writing - review & editing. **Sven Haller:** Methodology, Writing - review & editing. **Fabienne Picard:** Funding acquisition, Project administration, Conceptualization, Writing - review & editing, Supervision.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2020.116729>.

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