NeuroImage 199 (2019) 143–152

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Cholinergic and serotonergic modulation of resting state functional brain connectivity in Alzheimer's disease

Bernadet L. Klaassens [a,b,c,d,*], Joop M.A. van Gerven [d], Erica S. Klaassen [d], Jeroen van der Grond [b], Serge A.R.B. Rombouts [a,b,c]

[a] Leiden University, Institute of Psychology, Leiden, the Netherlands
[b] Leiden University Medical Center, Department of Radiology, Leiden, the Netherlands
[c] Leiden University, Leiden Institute for Brain and Cognition, Leiden, the Netherlands
[d] Centre for Human Drug Research, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Alzheimer's disease
Acetylcholine
Serotonin
Functional connectivity
Resting state functional MRI

ABSTRACT

Disruption of cholinergic and serotonergic neurotransmitter systems is associated with cognitive, emotional and behavioural symptoms of Alzheimer's disease (AD). To investigate the responsiveness of these systems in AD we measured the effects of a single-dose of the selective serotonin reuptake inhibitor citalopram and acetylcholinesterase inhibitor galantamine in 12 patients with AD and 12 age-matched controls on functional brain connectivity with resting state functional magnetic resonance imaging. In this randomized, double blind, placebo-controlled crossover study, functional magnetic resonance images were repeatedly obtained before and after dosing, resulting in a dataset of 432 scans. Connectivity maps of ten functional networks were extracted using a dual regression method and drug vs. placebo effects were compared between groups with a multivariate analysis with signals coming from cerebrospinal fluid and white matter as covariates at the subject level, and baseline and heart rate measurements as confound regressors in the higher-level analysis (at $p < 0.05$, corrected). A galantamine induced difference between groups was observed for the cerebellar network. Connectivity within the cerebellar network and between this network and the thalamus decreased after galantamine vs. placebo in AD patients, but not in controls. For citalopram, voxelwise network connectivity did not show significant group × treatment interaction effects. However, we found default mode network connectivity with the precuneus and posterior cingulate cortex to be increased in AD patients, which could not be detected within the control group. Further, in contrast to the AD patients, control subjects showed a consistent reduction in mean connectivity with all networks after administration of citalopram. Since AD has previously been characterized by reduced connectivity between the default mode network and the precuneus and posterior cingulate cortex, the effects of citalopram on the default mode network suggest a restoring potential of selective serotonin reuptake inhibitors in AD. The results of this study also confirm a change in cerebellar connections in AD, which is possibly related to cholinergic decline.

1. Introduction

In Alzheimer's disease (AD), destruction of neural tissue leads to loss of cholinergic nuclei in the basal forebrain and depleted cholinergic innervation towards the cerebral cortex, thalamus and hippocampus (Mesulam and Geula, 1988; Muir, 1997; Schliebs and Arendt, 2011). Acetylcholinesterase inhibitors (AChEIs) prevent the breakdown of acetylcholine and are often used as drug treatment to improve the cognitive symptoms of AD (Pepeu and Giovannini, 2009; Soreq and Seidman, 2001). In addition, reduced 5-hydroxytryptamine (5-HT; serotonin) activity plays a role in the cognitive deterioration (Claeysen et al., 2015; Geldenhuys and Van der Schyf, 2011), as well as in behavioural and mood changes that frequently accompany AD (Meltzer et al., 1998; Ownby et al., 2006). The cholinergic and serotonergic systems act in concert with each other with regard to functions like learning and memory (McEntee and Crook, 1991; Richter-Levin and Segal, 1993; Riekkinen et al., 1994), further suggesting the involvement of both systems in AD.

* Corresponding author. Leiden University, Institute of Psychology Unit Methodology and Statistics, PO Box 9555, 2300 RB, Leiden, the Netherlands.
E-mail address: b.l.klaassens@fsw.leidenuniv.nl (B.L. Klaassens).

https://doi.org/10.1016/j.neuroimage.2019.05.044
Received 21 October 2018; Received in revised form 14 May 2019; Accepted 16 May 2019
Available online 18 May 2019

Single-dose administration of compounds that inhibit or excite synaptic activity can alter brain connectivity during rest, reflecting the responsiveness of neurotransmitter networks and related functions (Khalili-Mahani et al., 2015; Kleinloog et al., 2015; Niesters et al., 2014). This pharmacological 'challenge' technique is aimed at discovering the underlying neurobiological mechanisms behind drug action and neurotransmitter-related disease. The approach seems especially relevant for measuring deviant functional processes in AD, which is conceived as a disorder of both large-scale network disconnections (Delbeuck et al., 2003; Seeley et al., 2009) and decrements in neurotransmission.

Cholinergic network responses that have been studied so far substantiate the assumption that acetylcholine is involved in memory, learning and visual perception (Kang et al., 2014; Soreq and Seidman, 2001). A cholinergic challenge caused increased connectivity in healthy young subjects with regions that are implicated in visual processing, memory and attention (Klaassens et al., 2017a). Effects of AChEIs on connectivity in AD patients have only been examined after long-term cholinergic treatment, and show enhanced connectivity of the default mode network (DMN) and the interrelated hippocampus (Blautzik et al., 2016; Goveas et al., 2011; Griffanti et al., 2016; Li et al., 2012; Solé-Padullés et al., 2013; Zaidel et al., 2012). Despite the likelihood of disrupted serotonin transmission, serotonergic modulation of brain connectivity has not yet been studied in AD. Acute or short-term treatment with selective serotonin reuptake inhibitors (SSRIs) elicits reduced connectivity of the DMN and several other cortical and subcortical areas in healthy subjects (Klaassens et al., 2015; McCabe and Mishor, 2011; McCabe et al., 2011; Schaefer et al., 2014; Van de Ven et al., 2013; Van Wingen et al., 2014) and patients with a major depressive disorder (Li et al., 2013).

In this randomized, placebo-controlled, crossover study, we used resting state functional magnetic resonance imaging (RS-fMRI) to visualize cholinergic and serotonergic neurotransmitter networks in AD patients and age-matched controls. We hypothesized that single-dose AChEI and SSRI administration changes the functional integrity of neural networks differently in AD patients compared to controls, and that the altered connections would mostly apply to regions that are susceptible for AD related connectivity change such as the hippocampus, thalamus, precuneus and cingulate cortex (Hafkemeijer et al., 2012; Sheline and Raichle, 2013). The outcomes of this study will provide fundamental knowledge on biochemical pathology in dementia, which might eventually benefit drug development and efficacy in neurodegenerative diseases.

2. Material and methods

2.1. Subjects

We included 12 patients with mild AD and 12 gender- and age-matched controls. The clinical diagnosis of probable AD was established according to the revised criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 2011). Following these criteria, AD was diagnosed based on the presence of cognitive and behavioural symptoms as determined by objective cognitive assessment and history-taking, that interfere with functioning during work and usual activities, represent a decline from previous levels, are not due to delirium or other psychiatric disorders, and concern two of the five specified domains (memory impairment, executive dysfunction, impaired visuospatial abilities, impaired language functions and changes in personality and behaviour). In addition, symptoms had an insidious onset, worsened over time and initial cognitive deficits included amnestic or non-amnestic decline. Supporting evidence of temporal lobe or parietal cortex atrophy was provided by computed tomography (CT) or structural MRI scans. All AD patients participating in this study were recently diagnosed and had mild to moderate cognitive deficits. To ensure the exclusion of severe AD cases, patients with a Mini Mental State Examination (MMSE) score (Folstein et al., 1975) below 18 were not included in the study. Furthermore, they were assessed by a physician (i.e. neurologist, geriatrician) as mentally capable of understanding the implications of study participation. The age-matched subjects who served as controls had an MMSE score between 28 and 30 (see Table 1 for demographics). All subjects underwent a thorough medical screening at the Centre for Human Drug Research (CHDR) to investigate whether they met the inclusion and exclusion criteria. They had a normal history of physical health and were able to refrain from using nicotine and caffeine during study days. Exclusion criteria included positive drug or alcohol screen on study days, regular excessive consumption of alcohol (>4 units/day), caffeine (>6 units/day) or cigarettes (>5 cigarettes/day), use of concomitant medication 2 weeks prior to study participation and involvement in an investigational drug trial 3 months prior to administration. The study was approved by the medical ethics committee of the Leiden University Medical Centre (LUMC). Written informed consent was obtained from each subject prior to study participation.

2.2. Experimental design

This was a single centre, randomized, double blind, placebo-controlled crossover study with citalopram 30 mg and galantamine 8 mg (Klaassens et al., 2018). Each subject received citalopram, galantamine and placebo on 3 different days, with a washout period between study days of at least 7 days. Citalopram has an average time point of maximum concentration (T_{max}) of 2–4 h, with a half-life (T½) of 36 h. For galantamine, T_{max} = 1–2 h and T½ = 7–8 h. To correct for the different pharmacokinetic (PK) profiles, citalopram 20 mg was administered at T = 0 h, followed by a second dose of 10 mg at T = 1 h (if the first dose was tolerated). Galantamine was given as a single 8 mg dose at T = 2 h. Blinding was maintained by concomitant administration of double-dummy placebo's at all three time points. All subjects received an unblinded dose of granisetron 2 mg at T = −0.5 h, to prevent the most common drug-induced adverse effects of nausea and vomiting.

Six RS-fMRI scans were acquired during each study day, two at baseline and four after administering citalopram, galantamine or placebo (at T = 2.5, 3.5, 4.5 and 6 h) (Fig. 1). Each scan was followed by performance of computerized cognitive tasks (taken twice at baseline) on the NeuroCart® test battery, for quantifying pharmacological effects on the CNS (Dumont et al., 2005; Gijsman et al., 2002; Liem-Moolenaar et al., 2011). Our sample size was based on previous studies (Khalili-Mahani et al., 2012, 2015; Kleinloog et al., 2015; Klumpers et al., 2012; Niesters et al., 2012) that showed significant pharmacological effects in repeated measures designs with 12 subjects. By including multiple measurements during the T_{max} interval, this repeated measures profile increases the statistical power of the analysis and allows for identification of time related effects, associated with changing serum concentrations. On each study day, nine blood samples were taken during the course of the day to define the PK profile of citalopram, citalopram's active metabolite desmethylcitalopram and galantamine (Jacobs et al., 2010; Umegaki et al., 2009). Concentrations of cortisol and prolactin, which reflect central neuroendocrine effects of SSRIs and AChEIs (Cozanitis et al., 1980; Sagud

Table 1
Demographics of mild AD patients and controls.

	AD patients	Controls
N	12	12
Age (Mean ± SD)	74.0 ± 5.2	73.1 ± 5.2
Age range	65–81	64–79
Male/female	6/6	6/6
MMSE (Mean ± SD)	22.3 ± 2.5	29.3 ± 0.9
MMSE range	19–28	28–30
BMI (kg/m^2) range	22–30	22–31

Abbreviations: AD = Alzheimer's disease; SD = standard deviation; MMSE = Mini Mental State Examination; BMI = body mass index.

et al., 2002; von Bardeleben et al., 1989), were investigated as well to indicate neuropharmacological effects in both groups.

2.3. Outcome measures

2.3.1. Pharmacokinetics

PK parameters for citalopram, galantamine and citalopram's active metabolite desmethylcitalopram were calculated using a non-compartmental analysis to validate the choice of time points of pharmacodynamic endpoints (RS-fMRI, NeuroCart®, neuroendocrine measures). Blood samples were collected in 4 mL EDTA plasma tubes at baseline and 1, 2, 2.5, 3, 3.5, 4.5 and 6 h post dosing, centrifuged (2000 *g* for 10 min) and stored at −40 °C until analysis with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

2.3.2. Neuroendocrine variables

Blood samples were obtained to determine cortisol and prolactin concentrations. Serum samples were taken in a 3.5 mL gel tube at baseline (twice) and 1, 2, 2.5, 3.5, 4.5 and 6 h post dosing, centrifuged (2000 *g* for 10 min) and stored at −40 °C until analysis. Serum concentrations were quantitatively determined with electrochemiluminescence immunoassay.

2.3.3. NeuroCart® test battery

Each RS-fMRI scan was followed by functional CNS measures in a separate room using the computerized NeuroCart® test battery measuring alertness, mood and calmness (Visual Analogue Scales (VAS) Bond & Lader), nausea (VAS Nausea), vigilance and visual motor performance (Adaptive Tracking task), reaction time (Simple Reaction Time task), attention, short-term memory, psychomotor speed, task switching and inhibition (Symbol Digit Substitution Test and Stroop task), working memory (N-back task) and memory imprinting and retrieval (Visual Verbal Learning Test) (Bond and Lader, 1974; Borland and Nicholson, 1984; Laeng et al., 2005; Lezak, 2004; Lim et al., 2008; Norris, 1971; Rogers et al., 2004; Stroop, 1935; Wechsler, 1981). The Visual Verbal Learning Test was only performed once during each day (at 3 and 4 h post dosing) as the test itself consists of different trials (imprinting and retrieval). Duration of each series of NeuroCart® brain function tests was approximately 20 min. To minimize learning effects, training for the NeuroCart® tasks occurred during the screening visit within 3 weeks prior to the first study day.

2.3.4. Imaging

Scanning was performed at the LUMC on a Philips 3.0 T Achieva MRI scanner (Philips Medical System, Best, The Netherlands) using a 32-channel head coil. All subjects were asked to close their eyes while staying awake prior to each RS-fMRI session at baseline and after drug or placebo administration on all three study days. T1-weighted anatomical images were only acquired at baseline for registration purposes as described in section 2.4.3.1. To facilitate registration to the anatomical image, each RS-fMRI scan was followed by a high-resolution T2*-weighted echo-planar scan.

RS-fMRI data were obtained with T2*-weighted echo-planar imaging (EPI) with the following scan parameters: 220 whole brain volumes, repetition time (TR) = 2180 ms; echo time (TE) = 30 ms; flip angle = 85°; field-of-view (FOV) = 220 × 220 × 130 mm; in-plane voxel resolution = 3.44 × 3.44 mm, slice thickness = 3.44 mm, including 10% inter-slice gap; acquisition time 8 min. For 3D T1-weighted MRI the following parameters were used: TR = 9.1 ms; TE = 4.6 ms; flip angle = 8°; FOV = 224 × 177 × 168 mm; in-plane voxel resolution = 1.17 × 1.17 mm; slice thickness = 1.2 mm; acquisition time 5 min. Parameters of high-resolution T2*-weighted EPI scans were set to: TR = 2200 ms; TE = 30 ms; flip angle = 80°; FOV = 220 × 220 × 168 mm; in-plane voxel resolution = 1.96 × 1.96 mm; slice thickness = 2.0 mm; acquisition time 30 s.

2.4. Statistical analysis

2.4.1. Pharmacokinetics

Maximum plasma concentrations (C_{max}) and time of C_{max} (T_{max}) were obtained directly from the plasma concentration data. The area under the plasma concentration vs. time curve was calculated from time zero to the time of the last quantifiable measured plasma concentration ($AUC_{0\text{-last}}$). To investigate differences between groups, PK parameters were analysed using a mixed effects model with group as fixed effect (SAS for Windows V9.4; SAS Institute, Inc., Cary, NC, USA).

2.4.2. Neuroendocrine variables and NeuroCart® test battery

Treatment (drug vs. placebo) x group (AD patients vs. controls) interaction effects on cortisol and prolactin concentrations and Neurocart® measures were investigated using a mixed effects model with treatment, time, group, visit, treatment by time, treatment by group and treatment by group by time as fixed effects, subject, subject by treatment and subject by time as random effects and the average of the period baseline (pre-dose) values as covariate (SAS for Windows V9.4; SAS Institute, Inc., Cary, NC, USA). The neuroendocrine data and data of the Simple Reaction Time task were not normally distributed and therefore log-transformed before analysis and back transformed after analysis. The data of the Visual Verbal Learning test were analysed using a mixed effects model with treatment, group, visit and treatment by group as fixed effects and subject as random effect.

2.4.3. Imaging

All fMRI analyses were performed using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL, Oxford, United Kingdom) version 5.0.7 (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009).

2.4.3.1. Data preprocessing. Each individual functional EPI image was inspected, brain-extracted and corrected for geometrical displacements due to head movement with linear (affine) image registration (Jenkinson et al., 2002; Smith, 2002). Head movement was also inspected by calculating the mean framewise displacement of each RS-fMRI image (see Supplementary Table 1) (Power et al., 2012), which were all below half a voxel's width. Images were spatially smoothed with a 6 mm full-width half-maximum Gaussian kernel. Registration parameters for non-smoothed data were estimated to transform fMRI scans into standard

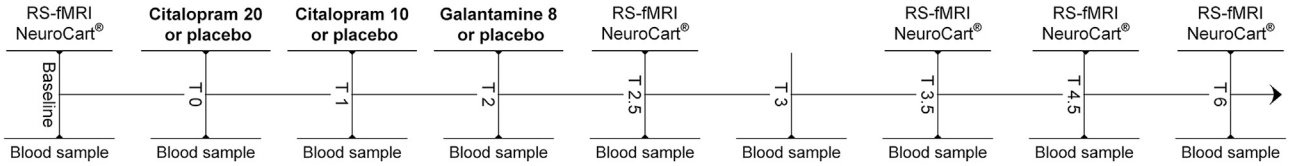

Fig. 1. Schematic overview of a study day. Each subject received citalopram, galantamine and placebo on three different days. At baseline, two RS-fMRI scan were acquired, followed by the NeuroCart® CNS test battery. After drug administration, four more RS-fMRI scans were acquired at time points T = 2.5, 3.5, 4.5 and 6 h post dosing, each time followed by the NeuroCart® test battery. During the day, nine blood samples were taken to measure the concentrations of citalopram, desmethylcitalopram, galantamine, cortisol and prolactin. On each study day there were three moments of administration. The second administration only took place when subjects tolerated the first dose well (did not vomit or feel too nauseous).

space and co-registered with the brain extracted high resolution T2*-weighted EPI scans (with 6 degrees of freedom) and T1-weighted images (using the Boundary-Based-Registration method) (Greve and Fischl, 2009). The T1-weighted scans were non-linearly registered to the MNI 152 standard space (the Montreal Neurological Institute, Montreal, QC, Canada) using FMRIB's Nonlinear Image Registration Tool. Registration parameters were estimated on non-smoothed data to transform fMRI scans into standard space after Automatic Removal Of Motion Artifacts based on Independent Component Analysis (ICA-AROMA vs0.3-beta). ICA-AROMA attempts to identify and remove motion related noise components by investigating its temporal and spatial properties. As recommended, high pass temporal filtering (with a high pass filter of 150 s) was applied after denoising the fMRI data with ICA-AROMA (Pruim et al., 2015a, 2015b).

2.4.3.2. Estimation of network connectivity. RS-fMRI networks were extracted from each individual denoised RS-fMRI dataset (24 subjects x 3 days × 6 scans = 432 datasets) with a dual regression analysis (Beckmann et al., 2009; Filippini et al., 2009) based on 10 predefined standard network templates (Klaassens et al., 2015, 2017a). These standard templates have been identified using a data-driven approach (Smith et al., 2009) and comprise the following networks: three visual networks (consisting of medial, occipital pole, and lateral visual areas), default mode network, cerebellar network, sensorimotor network, auditory network, executive control network and left and right frontoparietal networks. Time series of white matter, measured from the centre of the corpus callosum, and cerebrospinal fluid (CSF), measured from the centre of the lateral ventricles, were added as confound regressors in this analysis to account for non-neuronal signal fluctuations (Birn, 2012).

With the dual regression method, spatial maps representing voxel-to-network connectivity were estimated for each dataset separately in two stages and used for higher level analysis. First, the weighted network maps were used in a spatial regression into each dataset. This stage generated 12 time series per dataset that describe the average temporal course of signal fluctuations of the 10 networks plus 2 confound regressors (CSF and white matter). Next, these time series were entered in a temporal regression into the same dataset, resulting in a spatial map per network per dataset with regression coefficients referring to the weight of each voxel being associated with the characteristic signal change of a specific network. The higher the value of the coefficient, the stronger the connectivity of this voxel with a given network.

For an overall impression of connectivity alterations during study days, mean *z*-values of these regression coefficients within networks were calculated for each group and study day separately. By comparing the average of the four post measurements with the average of the two baseline measurements it was semi-quantitatively inspected how the average connectivity within each network changed (increased vs. decreased) during study days. Fisher's exact test was applied to investigate differences between groups in the number of networks with a specific direction of this global connectivity change.

2.4.3.3. Higher level analysis. Local group × treatment interaction effects of citalopram and galantamine were investigated with non-parametric combination (NPC) as provided by FSL's Permutation Analysis for Linear Models tool (PALM vs94-alpha) (Pesarin, 1990; Winkler et al., 2014, 2016b) and as previously used to investigate differences in pharmacological effects between young and older adults (Klaassens et al., 2018). NPC is a multivariate method that offers the possibility to combine data of separate, possibly non-independent tests, such as our multiple time points, and investigate the presence of joint effects across time points, in a test that has fewer assumptions and is more powerful than repeated-measurements ANOVA or multivariate ANOVA (MANOVA).

First, tests were performed for each time point using 1000 synchronized permutations, followed by the fit of a generalized Pareto distribution to the tail of the approximation distribution, thus refining the *p*-values at the tail further than otherwise possible with a small number of permutations (Winkler et al., 2016a). More specifically, to investigate group × treatment interaction effects on voxelwise functional connectivity with each of the 10 functional networks, four two-sample *t*-tests (AD patients: drug - placebo vs. controls: drug - placebo) were performed for all post-dose time points (T = 2.5, 3.5, 4.5 and 6 h), with average heart rate (beats/m) per RS-fMRI scan as confound regressor (Khalili-Mahani et al., 2013). The average of the two baseline RS-fMRI scans was used as covariate as well, by adding the coefficient spatial map as a voxel-dependent regressor in the model. This will control for the confounding influence of possibly systematic individual differences and group differences at baseline level as recently analysed and described in Klaassens et al. (2017b). The same method was applied for additional investigation of treatment effects (drug vs. placebo) on the DMN within the group of AD patients and within the control group as was previously done for a group of young adults (Klaassens et al., 2017a). To that end, four one-sample *t*-tests (drug vs. placebo) were performed for all post-dose time points (T = 2.5, 3.5, 4.5 and 6 h), with average heart rate (beats/m) per RS-fMRI scan as confound regressor.

Second, to analyse effects across time, the tests for the four time points were combined non-parametrically via NPC using Fisher's combining function (Fisher, 1932) and the same set of synchronized permutations as mentioned above. A liberal mask was used to investigate voxels within the MNI template, excluding voxels belonging to CSF. Threshold-free cluster enhancement was applied to the tests at each time point and after the combination, and the resulting voxelwise statistical maps were corrected for the familywise error rate using the distribution of the maximum statistic (Smith and Nichols, 2009; Winkler et al., 2014). Voxels were considered significant at $p < 0.05$, corrected.

3. Results

3.1. Pharmacokinetics

PK parameters (T_{max}, C_{max} and $AUC_{0\text{-last}}$) in AD patients and controls are summarized in Table 2. There were no PK differences between AD patients and controls. Fig. 2 shows the individual and median citalopram and galantamine PK time profiles.

3.2. Neuroendocrine variables and NeuroCart® test battery

There were no significant group × treatment interaction effects of citalopram and galantamine on cortisol and prolactin. See Supplementary Fig. 1 for cortisol and prolactin levels in AD patients and controls. For an overview of all NeuroCart® results, we refer the reader to Supplementary Table 2. No significant group × treatment interaction effects were observed for citalopram or galantamine.

3.3. Imaging

3.3.1. Global connectivity changes

Calculations of the pre and post treatment average connectivity (mean *z*-values) per network, group and treatment are summarized in Table 3. Delta scores show that on placebo days connectivity reduced from pre to post measurement for 6 of the 10 networks in patients with AD and for 4 of the 10 networks in controls. Fisher's exact test did not lead to a significant difference in prevalence in number of networks that showed a decrease in average connectivity (6/10 vs. 4/10).

Table 3 also presents the pre-post changes in global connectivity during treatment days. The diurnal patterns of network alterations after galantamine administration were similar between groups as well. The prevalence in number of networks that showed a decrease in connectivity in controls (3/10) vs. patients with AD (7/10) did not lead to a significant difference.

In contrast to placebo and galantamine study days, group differences

Table 2
Pharmacokinetics of citalopram, desmethylcitalopram and galantamine in AD patients and controls.

PK parameters	Citalopram			Desmethylcitalopram			Galantamine		
	Mean ± SD		Contrasts (*p*-value)	Mean ± SD		Contrasts (*p*-value)	Mean ± SD		Contrasts (*p*-value)
	AD patients	Controls		AD patients	Controls		AD patients	Controls	
T_{max}	3.6 ± 1.2	3.4 ± 1.1	0.527	4.3 ± 1.4	4.0 ± 1.3	0.491	5.0 ± 0.9	4.5 ± 1.1	0.306
C_{max}	38.8 ± 4.5	41.8 ± 11.7	0.147	3.0 ± 1.3	3.5 ± 1.8	0.395	36.4 ± 8.0	41.8 ± 12.2	0.324
$AUC_{0\text{-last}}$	153.0 ± 19.0	165.0 ± 43.6	0.150	11.1 ± 5.3	13.3 ± 7.1	0.366	84.7 ± 35.7	104.0 ± 40.2	0.151

Abbreviations: AD = Alzheimer's disease; PK = pharmacokinetic; Tmax = time point (h) of maximum concentration; Cmax = maximum concentration (ng/mL); AUC0-last = area under the plasma concentration versus time curve (ng*h/mL).

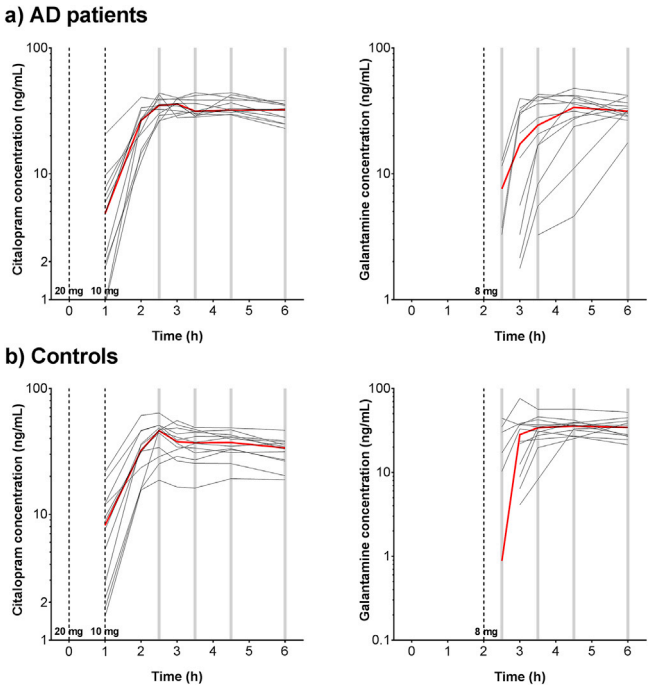

Fig. 2. Pharmacokinetic profiles. Median (red line) and individual (black lines) PK profiles for citalopram (left) and galantamine (right) concentrations in AD patients (a) and controls (b). Vertical bars illustrate the timing of RS-fMRI acquisition post drug administration. Observations below limit of quantification were dismissed.

were observed during citalopram occasions. After citalopram administration, reduced connectivity was consistently observed for all 10 networks in controls, but only in 4 out of 10 networks in patients with AD. A prevalence of 10/10 vs. 4/10 networks that showed a decrease in connectivity was tested significant ($p < 0.05$).

3.3.2. Local differences in drug effects between AD patients and controls

A significant group × treatment interaction effect of galantamine was found for connectivity within the cerebellar network (see Table 4 for specifications and extent of significant effects). In AD patients, galantamine induced a decrease in connectivity of the cerebellar network with the cerebellum, thalamus and brain stem (interaction and main effects are shown in Fig. 3). In controls, galantamine did not induce connectivity alterations with the cerebellar network.

There were no significant differences in network effects of citalopram vs. placebo between AD patients and controls. Within-group analyses showed that citalopram significantly increased connectivity between the DMN and precuneus/posterior cingulate cortex (PCC) compared to placebo in AD patients, but not in controls (Fig. 4). Table 4 shows specifications and extent of significant effects.

4. Discussion

We investigated functional network alterations after a serotonergic and cholinergic challenge to gain insight into disruptions of neurotransmitter pathways in AD. Comparing AD patients with age-matched controls, we found a significant group × treatment interaction effect after administration of the AChEI galantamine on cerebellar network connectivity. Galantamine induced a local decrease in cerebellar connectivity in AD patients, but not in controls. The SSRI citalopram did not alter regional connectivity differently between groups. However, after citalopram intake, the observed overall effect of lowered connectivity among all networks in controls was absent in AD. In addition, although there was no local interaction effect, a citalopram intensified DMN-precuneus/PCC connection was only observed in the AD group. To guarantee appropriate comparison between groups, PK properties and neuroendocrine effects of both compounds were investigated as well, and reassuring of equal absorption rates and hormone fluctuations (Seifritz et al., 1996), that might otherwise have led to spurious group × treatment interactions.

4.1. Galantamine effects

This study is the first to investigate single-dose galantamine effects on resting state functional connectivity in AD, providing novel information on acute cholinergic alterations of related neural circuits that might underlie the cognitive improvements during chronic treatment. Acute AChEI administration usually does not lead to cognitive enhancement in healthy subjects or AD (Lanctot et al., 2003; Repantis et al., 2010). Correspondingly, we did not find convincing effects of galantamine on any NeuroCart® task. This might be the consequence of our small sample size, which is an obvious restriction of the study. However, despite this limitation, galantamine did result in a diminished cerebellar network response in AD patients compared to controls, suggesting that RS-fMRI could be a sensitive method for measuring acute pharmacological effects. Most studies in the literature describe enhanced resting state connectivity after AChEI intake in AD patients (Blautzik et al., 2016; Goveas et al., 2011; Griffanti et al., 2016; Li et al., 2012; Solé-Padullés et al., 2013; Zaidel et al., 2012). Contrary to our single-dose administration these studies all pertain to long-term cholinergic treatment. It is possible that neuroplasticity and modulation of cholinergic pathways over a longer period of AChEI treatment result in opposite findings. For example, increases in posterior DMN connectivity of AD patients as described by Blautzik et al. (2016) were prevalent after 12 but not after 6 months of galantamine treatment, which was interpreted as indicating an insufficient time delay of 6 months to measure cholinergic effects. Solé-Padullés et al. (2013) demonstrated significant increased DMN connectivity with the right-hemispheric parahippocampal gyrus in treated compared to untreated AD patients after 12 weeks of AChEI treatment but were not able to find longitudinal effects on connectivity with the DMN within treated patients. Of their 8 treated subjects, 5 even showed stable or increased connectivity when they used this area as region of interest.

Table 3
Mean *z*-scores within networks per group, per treatment, pre (average of 2 baseline measurements) and post (average of 4 measurements) drug administration, and delta scores of the difference between pre and post measurements.

Group	AD patients								Controls							
Treatment	Placebo			Citalopram			Galantamine			Placebo			Citalopram			Galantamine		
Measurement	pre	post	Δ	pre	post	Δ	pre	post	Δ	pre	post	Δ	pre	post	Δ	pre	post	Δ
Visual network (medial)	7.13	7.07	−0.06	6.78	7.27	0.49	6.06	6.38	0.32	4.58	5.71	1.13	5.64	4.92	−0.72	4.97	4.32	−0.65
Visual network (occipital)	5.18	5.40	0.22	4.82	5.56	0.74	4.77	4.72	−0.05	3.69	4.25	0.56	4.50	4.35	−0.15	4.03	3.74	−0.29
Visual network (lateral)	4.64	4.81	0.17	4.57	4.96	0.39	4.32	4.16	−0.16	3.82	4.13	0.31	4.57	4.14	−0.43	3.51	3.91	0.4
Default mode network	6.66	5.91	−0.75	6.42	6.55	0.13	6.76	6.20	−0.56	6.82	6.59	−0.23	6.98	6.70	−0.28	6.93	6.29	−0.64
Cerebellar network	3.55	3.94	0.39	3.01	3.61	0.6	3.11	2.85	−0.26	3.50	2.87	−0.63	2.83	2.78	−0.05	2.69	3.03	0.34
Sensorimotor network	4.23	4.71	0.48	4.68	4.46	−0.22	4.01	4.32	0.31	3.92	4.04	0.12	4.56	3.54	−1.02	3.72	3.69	−0.03
Auditory network	4.60	4.34	−0.26	4.27	4.29	0.02	4.36	4.24	−0.12	4.20	4.27	0.07	4.75	4.07	−0.68	4.28	4.01	−0.27
Executive control network	4.61	4.09	−0.52	4.42	3.80	−0.62	3.63	4.06	0.43	3.74	4.11	0.37	3.98	3.50	−0.48	3.67	3.96	0.29
Frontoparietal network right	4.55	4.38	−0.17	4.59	4.27	−0.32	4.62	3.96	−0.66	4.83	4.29	−0.54	4.82	4.61	−0.21	5.17	4.48	−0.69
Frontoparietal network left	4.94	4.18	−0.76	4.60	4.35	−0.25	4.78	4.57	−0.21	5.12	4.87	−0.25	5.45	5.21	−0.24	5.60	5.15	−0.45

4.2. Galantamine and the cerebellar network

The reduction of cerebellar-thalamic connectivity in patients with AD was partly due to an increase in cerebellar connectivity after placebo as opposed to a decrease after galantamine. This observation underlines the importance of implementing a placebo-controlled design to investigate drug effects in comparison to diurnal fluctuations that are observed on placebo days and, as is the case for the cerebellar network, might show opposite patterns. Similarly, we found the average cerebellar network connectivity to decrease after placebo and to increase after galantamine administration. The average change in global cerebellar network connectivity during placebo days in the control group also indicates a normalizing effect of galantamine in AD patients, since the mean connectivity after galantamine in patients (mean $z = 2.85$) equals the mean connectivity after placebo days in controls (mean $z = 2.87$) instead of after placebo in patients with AD (mean $z = 3.94$).

It is increasingly recognized that the cerebellum is involved in cognitive and affective processes that are affected in neurodegenerative diseases (Colloby et al., 2014; Samson and Claassen, 2017; Thomann et al., 2008). Certain parts of the cerebellum have extensive fibre connections with specific cerebral areas (Buckner et al., 2011; Glickstein and Doron, 2008) and previous studies have demonstrated robust structural cerebellar-cortical atrophy connections (Guo et al., 2016) and lower functional connectivity within a network consisting of the basal ganglia and cerebellum (Binnewijzend et al., 2012) in dementia. It has also been suggested that the cerebellum contributes to the DMN, salience and executive control networks, indicating that cortico-cerebellar pathways are involved in executive and salience functioning, episodic memory and self-reflection (Habas et al., 2009), and might therefore play a role in symptoms as seen in AD.

The results of our study might relate to an association between cholinergic pathways and cerebellar connections in AD. Despite a lack of dense cholinergic innervation of the mammalian cerebellum, acetylcholine seems to excite the cerebellum's muscarinic Purkinje cells and mossy fibres that are rich in choline acetyltransferase (Jaarsma et al., 1996, 1997; Kwong et al., 2000; McCance and Phillis, 1968; Mount et al., 1994). The observed depletion of dendritic Purkinje neurons in AD (Mavroudis et al., 2010) possibly accounts for altered cholinergic projections after galantamine as shown in our study, which is also supported by delayed loss of Purkinje cells after AChEI treatment (Mount et al., 1994; Seo et al., 2014). Apart from cortical cholinergic input originating in the nucleus basalis of Meynert, a prominent cholinergic cell group in the brain stem projects towards the thalamus (Heckers et al., 1992; McCance et al., 1968). The thalamus receives input from cerebellar nuclei, which in turn sends signals to all association areas of the cerebrum, including the prefrontal cortex (Palesi et al., 2015). In line with these pathways the observed decreased functional connections between the cerebellum, thalamus and brain stem in our mild AD group might represent diminished cholinergic trajectories in AD, which may be related to neuronal loss (Guo et al., 2016). However, caution is needed in this interpretation, since the exact relation between connectivity change and neurobiological effects has to be determined with more certainty.

4.3. Citalopram effects on cognitive functions

Citalopram did not affect any behavioural or cognitive state as measured with the NeuroCart® battery differently between both groups. Again, this might be due to our relatively small sample size. Moreover, and most importantly, SSRIs are known to produce very limited behavioural and cognitive change in wake resting conditions after single-dose administration (Dumont et al., 2005), despite immediate neural effects. We included the NeuroCart® tests as outcome measures to investigate the sensitivity of RS-fMRI to pharmacological challenges as a method to examine the role of neurotransmitter systems in AD and to better understand the neural bases of drug effectiveness. SSRIs are traditionally not used as medication for cognitive symptoms, but have been proposed

Table 4
Overview of significant citalopram and galantamine effects on functional connectivity as estimated with threshold-free cluster enhancement ($p < 0.05$, corrected).

Network effect	Region (Harvard-Oxford or Cerebellar atlas)		z*	x	y	z	# voxels
Cerebellar network (galantamine: AD patients > controls)	R	Cerebellum (lobules I-VI)	4.25	20	−42	−38	414
	L	Cerebellum (lobule VI)	3.91	−26	−48	−34	106
	R	Cerebellum (crus I and II)	3.91	20	−84	−26	9
Cerebellar network (AD patients: galantamine < placebo)	R	Cerebellum (lobules I-VI, IX, crus I), middle and inferior temporal gyrus, fusiform gyrus, temporal occipital fusiform cortex, parahippocampal gyrus	4.22	50	−34	−10	3108
	L	Cerebellum (lobules IX, V, VI, crus I)	3.95	−12	−56	−34	540
	L	Thalamus	4.00	−12	−12	6	168
	R	Inferior frontal gyrus, pars opercularis; precentral gyrus	4.50	36	14	22	110
	M	Brain stem	3.66	−4	−26	−24	66
	L	Thalamus, brain stem	4.08	−8	−30	−2	22
	R	Thalamus	4.03	18	−8	10	7
	L	Cerebellum (lobule VIIb, crus II)	2.85	−26	−72	−50	6
	R	Caudate	4.05	16	10	4	1
Default mode network (AD patients: citalopram > placebo)	L/R/M	Precuneus, PCC	4.34	−6	−72	−26	685
	R	Intracalcarine cortex, precuneus	3.54	4	−64	14	153

Abbreviations: AD = Alzheimer's disease; L = left; R = right; M = midline; PCC = posterior cingulate cortex. Voxel dimension = 2 mm × 2 mm x 2 mm (voxel volume 0.008 mL). * = standardized *z*-value of the uncorrected peak Fisher-statistic (NPC) within regions.

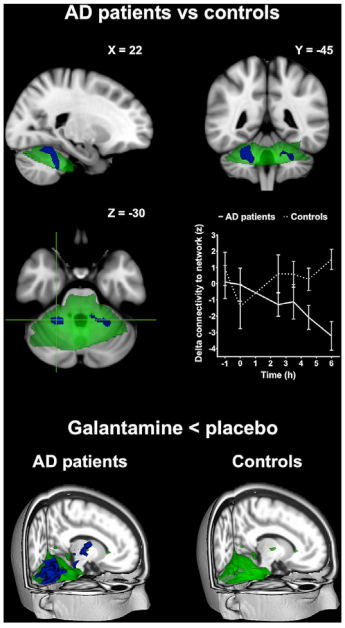

Fig. 3. Galantamine effects on functional network connectivity. A different effect on connectivity in AD patients compared to controls after galantamine vs. placebo within the cerebellar network (shown in green) for regions as shown in blue (top). The included plot visualizes the corresponding average time profiles of changes in functional connectivity per group for galantamine - placebo conditions (delta *z*-values with standard errors of the mean as error bars). The 3D images (bottom) show main galantamine effects per group. In AD patients, connectivity between the cerebellar network (green) and regions in blue was decreased, whereas no effect was found within the controls. Coronal and axial slices are displayed in radiological convention (left = right).

to treat emotional disturbances and agitation, which in many AD patients are an integral part of the disease (Leonpacher et al., 2016; Nyth and Gottfries, 1990; Porsteinsson et al., 2014). The included participants, motivated to comply with our intensive study program, were perhaps not representative of patients with AD with additional neuropsychiatric impairment, lowering the chance on a differentiated responsiveness of their serotonergic systems. Potentially, 5-HT hypofunction is also involved in cognitive disturbances of AD, although studies on the effect of SSRI administration on these aspects in AD patients are scarce (Schmitt et al., 2006). Combining AChEI treatment with an SSRI seems to improve global cognitive functioning in AD compared to AChEI treatment alone (Mowla, 2009), indicating a beneficial interaction between cholinergic and serotonergic stimulation, which is in line with observations on the receptor level (Buhot et al., 2000). Although single-dose administration of SSRIs has a limited measurable impact on healthy subjects in resting conditions, it has been well established that SSRIs cause changes in emotional bias in both healthy volunteers (Harmer et al., 2003) and depressed patients (Harmer et al., 2009b). These studies suggest that SSRIs cause acute improvements in emotional bias, which might contribute to the slow resolution of mood impairment (Harmer et al., 2009a). According to this hypothesis, the therapeutic activity of CNS-active drugs is not only dependent on its neuropharmacological mechanism, but also on its interaction with (abnormal) neuronal processes. However, there is much less evidence that similar interactions play a role in other situations, like delayed effects of acute cholinergic treatment on dementia. Studies of the acute effects of a CNS-active drug on network connectivity in unchallenged conditions can provide a basis for a better understanding of its long-term therapeutic effects. At any rate, our findings confirm the limited cognitive effects of single-dose SSRI administration (Dumont et al., 2005; Van Laar et al., 1995). A slight worsening of performance on two subtests of the N-back in the control group was most likely due to chance. It may also be a reflection of a non-linear dose-response, as small immediate memory improvements are most consistently observed in a low (therapeutic) dose range of SSRIs (Dumont et al., 2005).

4.4. Connectivity change after citalopram

We did not find any citalopram induced network differences between patients with AD and controls. However, since single-dose serotonergic stimulation in non-AD subjects mainly shows effects on DMN connectivity, and DMN coherence is most often found to be altered in AD, we examined drug effects on DMN connectivity within each group separately. An increase in DMN-precuneus/PCC connectivity after citalopram was found in the AD group, which could not be detected within the control group. We also observed a significant difference between AD patients and controls in the number of networks that showed a decrease vs. increase in connectivity after citalopram. The control group showed a reduction in connectivity after citalopram compared to baseline for all 10 networks, whereas this was only the case for 4 networks in the AD group. It is remarkable that we found this global connectivity to be enhanced after serotonergic stimulation in AD because previous studies almost uniformly show diminished network coherence after SSRI administration in healthy (Klaassens et al., 2015, 2017a; McCabe and Mishor, 2011; McCabe et al., 2011; Schaefer et al., 2014; Van Wingen et al., 2014) and depressed subjects (Li et al., 2013).

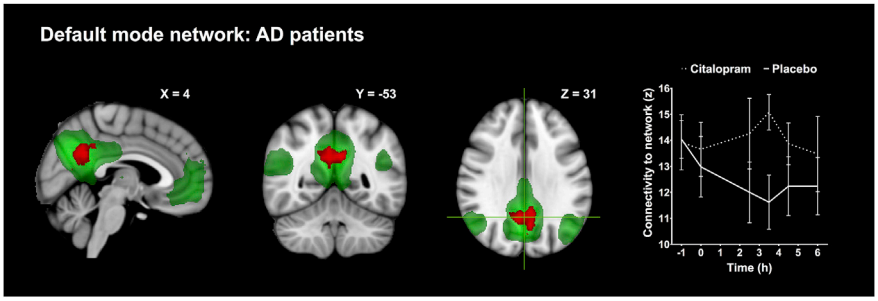

Fig. 4. Citalopram effects on functional network connectivity. Increased connectivity in AD patients after citalopram vs. placebo was observed within the DMN (shown in green) for the precuneus/PCC (shown in red). Plots visualize the corresponding average time profiles of changes in functional connectivity for citalopram (dotted line) and placebo (continuous line) conditions (*z*-values with standard errors of the mean as error bars). Coronal and axial slices are displayed in radiological convention (left = right).

Notably, depression is mainly characterized by increased connectivity (Sundermann et al., 2014), which may explain a lowering in connectivity after SSRI intake as antidepressant effect. AD however, is defined by decreased DMN-precuneus/PCC connectivity (Binnewijzend et al., 2012; Damoiseaux et al., 2012; Sheline et al., 2010; Tahmasian et al., 2015). The precuneus and PCC, both part of the DMN, are specifically implicated in symptomatology of AD such as impaired episodic memory retrieval, self-consciousness and visual-spatial imagery (Cavanna and Trimble, 2006; Karas et al., 2007; Rombouts et al., 2005; Sperling et al., 2010; Zhang and Li, 2012) and opposite findings after pharmacological enhancement in this study might indicate beneficial neurochemical effects in AD. Our observations are concordant with the effects of memantine, an N-methyl-d-aspartate (NMDA) receptor antagonist, which is used to treat moderate and severe cases of AD. Similar to our results, memantine has been shown to strengthen connectivity of the DMN with the precuneus in AD, which was interpreted as representing regularization of glutamatic levels that, in effect, leads to increased brain metabolic activity (Lorenzi et al., 2011). Although evidence on the efficacy of SSRIs as a treatment for cognitive symptoms of dementia is limited, several studies have demonstrated that serotonin might be an important target of pharmacological intervention. The serotonin antagonist and reuptake inhibitor trazodone hydrochloride has recently been discovered as a potential new disease-modifying treatment for dementia by arresting the unfolded protein response, and thereby neurodegenerative cell loss, in mice (Halliday et al., 2017). Another promising feature of SSRIs is the ability to suppress generation of beta amyloid in CSF of mice and human volunteers (Sheline et al., 2014), which implies the potential to prevent accumulation of beta amyloid, which has also been found in the precuneus of AD patients (Mintun et al., 2005).

5. Conclusions

Whether serotonin dysregulation in AD mostly contributes to behavioural or cognitive symptoms, or both, has yet to be sorted out. The absence of group × treatment interaction effects after administering citalopram points to relatively similar serotonergic systems in AD patients and controls. Our single-dose approach makes it difficult to relate connectivity changes after drug administration directly to behavioural effects. Behavioural challenges of emotional systems are probably required to elicit drug-induced effects on emotional circuitries. However, studies under resting state conditions are important, to allow further resolution of the interactions between serotonergic enhancement and emotional processing. This will ultimately also demand for long-term treatment paradigms and larger sample sizes in clinical populations. Nevertheless, our results suggest that SSRI administration has an enhancing effect on DMN-precuneus/PCC connectivity, which has been shown to be decreased in AD (Hafkemeijer et al., 2012). This opposite finding indicates that SSRIs might have an improving effect on memory, self-referential processes and/or visual-spatial functions. We also confirm the significance of a cerebellar network in AD (Guo et al., 2016), which has been largely neglected within dementia research, but might be an important component associated with cholinergic decline. A challenge for the future is to unravel how the acute response to these compounds develops over a longer treatment period and if this response could be predictive for treatment efficacy in AD.

Acknowledgements

We are thankful for the assistance of the Alrijne Hospital Leiden, Stichting Alzheimer Nederland and GGZ Rivierduinen Leiden in the recruitment of AD patients. Helene van Gorsel, Jasper Stevens and Jules Heuberger (CHDR) are acknowledged for medical support and contribution to the non-compartmental analysis of pharmacokinetic parameters. This project was funded by the Netherlands Initiative Brain and Cognition (NIHC), a part of the Netherlands Organisation for Scientific Research (NWO) (grant number 056-13-016). Serge Rombouts was supported by a VICI grant from NWO (grant number 016-130-677).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.05.044.

References

Beckmann, C.F., Mackay, C.E., Filippini, N., Smith, S.M., 2009. Group Comparison of Resting-State FMRI Data Using Multi-Subject ICA and Dual Regression. OHBM.
Binnewijzend, M.A.A., Schoonheim, M.M., Sanz-Arigita, E., Wink, A.M., van der Flier, W.M., Tolboom, N., Adriaanse, S.M., Damoiseaux, J.S., Scheltens, P., van Berckel, B.N.M., Barkhof, F., 2012. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol. Aging 33 (9), 2018–2028.
Birn, R.M., 2012. The role of physiological noise in resting-state functional connectivity. Neuroimage 62 (2), 864–870.
Blautzik, J., Keeser, D., Paolini, M., Kirsch, V., Berman, A., Coates, U., Reiser, M., Teiper, S.J., Meindl, T., 2016. Functional connectivity increase in the default-mode network of patients with Alzheimer's disease after long-term treatment with Galantamine. Eur. Neuropsychopharmacol. 26 (3), 602–613.
Bond, A., Lader, M., 1974. Use of analog scales in rating subjective feelings. Br. J. Med. Psychol. 47 (3), 211–218.
Borland, R.G., Nicholson, A.N., 1984. Visual motor coordination and dynamic visual-acuity. Br. J. Clin. Pharmacol. 18 (Suppl. 1), S69–S72.
Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (5), 2322–2345.
Buhot, H.C., Martin, S., Segu, L., 2000. Role of serotonin in memory impairment. Ann. Med. 32 (3), 210–221.
Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583.
Claeysen, S., Bockaert, J., Giannoni, P., 2015. Serotonin: a new hope in Alzheimer's disease? ACS Chem. Neurosci. 6 (7), 940–943.
Colloby, S.J., O'Brien, J.T., Taylor, J.P., 2014. Patterns of cerebellar volume loss in dementia with Lewy bodies and Alzheimer's disease: a VBM-DARTEL study. Psychiat. Res.-Neuroim. 223 (3), 187–191.
Cozanitis, D., Dessypris, A., Nuuttila, K., 1980. The effect of galanthamine hydrobromide on plasma ACTH in patients undergoing anesthesia and surgery. Acta Anaesthesiol. Scand. 24 (3), 166–168.
Damoiseaux, J.S., Prater, K.E., Miller, B.L., Greicius, M.D., 2012. Functional connectivity tracks clinical deterioration in Alzheimer's disease. Neurobiol. Aging 33 (4), 828.e19-828.e30.
Delbeuck, X., Van der Linden, M., Collette, F., 2003. Alzheimer's disease as a disconnection syndrome? Neuropsychol. Rev. 13 (2), 79–92.
Dumont, G.J.H., de Visser, S.J., Cohen, A.F., van Gerven, J.M.A., 2005. Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. Br. J. Clin. Pharmacol. 59 (5), 495–510.
Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G.B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain

activity in young carriers of the APOE-ε4 allele. Proc. Natl. Acad. Sci. U.S.A. 106 (17), 7209–7214.
Fisher, R.A., 1932. Statistical Methods for Research Workers. Oliver and Boyd, Edinburgh.
Folstein, M., Folstein, S., McHugh, P., 1975. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Geldenhuys, W.J., Van der Schyf, C.J., 2011. Role of serotonin in Alzheimer's disease: a new therapeutic target? CNS Drugs 25 (9), 765–781.
Gijsman, H.J., van Gerven, J.M.A., Verkes, R.J., Schoemaker, R.C., Pieters, M.S.M., Pennings, E.J.M., Hessing, T.J., Cohen, A.F., 2002. Saccadic peak velocity and EEG as end-points for a serotonergic challenge test. Hum. Psychopharm. Clin 17 (2), 83–89.
Glickstein, M., Doron, K., 2008. Cerebellum: connections and functions. Cerebellum 7 (4), 589–594.
Goveas, J.S., Xie, C.M., Ward, B.D., Wu, Z.L., Li, W.J., Franczak, M., Jones, J.L., Antuono, P.G., Li, S.J., 2011. Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. J. Magn. Reson. Imaging 34 (4), 764–773.
Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. Neuroimage 48 (1), 63–72.
Griffanti, L., Wilcock, G.K., Voets, N., Bonifacio, G., Mackay, C.E., Jenkinson, M., Zamboni, G., 2016. Donepezil enhances frontal functional connectivity in Alzheimer's disease: a pilot study. Dement. Geriatr. Cogn. Dis. Extra 6 (3), 518–528.
Guo, C.C., Tan, R., Hodges, J.R., Hu, X.T., Sami, S., Hornberger, M., 2016. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain 139, 1527–1538.
Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M.D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29 (26), 8586–8594.
Hafkemeijer, A., van der Grond, J., Rombouts, S.A.R.B., 2012. Imaging the default mode network in aging and dementia. B.B.A.-Mol. Basis Dis. 1822 (3), 431–441.
Halliday, M., Radford, H., Zents, K.A.M., Molloy, C., Moreno, J.A., Verity, N.C., Smith, E., Ortori, C.A., Barrett, D.A., Bushell, M., Mallucci, G.R., 2017. Repurposed drugs targeting eIF2α-P-mediated translational repression prevent neurodegeneration in mice. Brain 140 (6), 1768–1783.
Harmer, C.J., Bhagwagar, Z., Perrett, D.I., Vollm, B.A., Cowen, P.J., Goodwin, G.M., 2003. Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology 28 (1), 148–152.
Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009a. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br. J. Psychiatry 195 (2), 102–108.
Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G.M., Cowen, P.J., 2009b. Effect of acute antidepressant administration on negative affective bias in depressed patients. Am. J. Psychiatry 166 (10), 1178–1184.
Heckers, S., Geula, C., Mesulam, M.M., 1992. Cholinergic innervation of the human thalamus: dual origin and differential nuclear distribution. J. Comp. Neurol. 325 (1), 68–82.
Jaarsma, D., Dino, M.R., Cozzari, C., Mugnaini, E., 1996. Cerebellar choline acetyltransferase positive mossy fibres and their granule and unipolar brush cell targets: a model for central cholinergic nicotinic neurotransmission. J. Neurocytol. 25 (12), 829–842.
Jaarsma, D., Ruigrok, T.J.H., Caffe, R., Cozzari, C., Levey, A.I., Mugnaini, E., Voogd, J., 1997. Cholinergic innervation and receptors in the cerebellum. Prog. Brain Res. 114, 67–96.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17 (2), 825–841.
Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. FSL. Neuroimage 62 (2), 782–790.
Kang, J.I., Huppe-Gourgues, F., Vaucher, E., 2014. Boosting visual cortex function and plasticity with acetylcholine to enhance visual perception. Front. Syst. Neurosci. 8, 172.
Karas, G., Scheltens, P., Rombouts, S., van Schijndel, R., Klein, M., Jones, B., van der Flier, W., Vrenken, H., Barkhof, F., 2007. Precuneus atrophy in early-onset Alzheimer's disease: a morphometric structural MRI study. Neuroradiology 49 (12), 967–976.
Khalili-Mahani, N., Chang, C., van Osch, M.J., Veer, I.M., van Buchem, M.A., Dahan, A., Beckmann, C.F., van Gerven, J.M.A., Rombouts, S.A.R.B., 2013. The impact of "physiological correction" on functional connectivity analysis of pharmacological resting state fMRI. Neuroimage 65, 499–510.
Khalili-Mahani, N., Niesters, M., van Osch, M.J., Oitzl, M., Veer, I., de Rooij, M., van Gerveng, J., van Buchem, M.A., Beckmann, C.F., Rombouts, S.A.R.B., Dahan, A., 2015. Ketamine interactions with biomarkers of stress: a randomized placebo-controlled repeated measures resting-state fMRI and PCASL pilot study in healthy men. Neuroimage 108, 396–409.
Khalili-Mahani, N., Zoethout, R.M.W., Beckmann, C.F., Baerends, E., de Kam, M.L., Soeter, R.P., Dahan, A., van Buchem, M.A., van Gerven, J.M.A., Rombouts, S.A.R.B., 2012. Effects of morphine and alcohol on functional brain connectivity during "resting state": a placebo-controlled crossover study in healthy young men. Hum. Brain Mapp. 33 (5), 1003–1018.
Klaassens, B.L., Rombouts, S.A.R.B., Winkler, A.M., van Gorsel, H.C., van der Grond, J., van Gerven, J.M.A., 2017a. Time related effects on functional brain connectivity after serotonergic and cholinergic neuromodulation. Hum. Brain Mapp. 38 (1), 308–325.
Klaassens, B.L., van Gerven, J.M.A., Klaassen, E.S., van der Grond, J., Rombouts, S.A.R.B., 2018. Serotonergic and cholinergic modulation of functional brain connectivity: a comparison between young and older adults. Neuroimage 169, 312–322.
Klaassens, B.L., van Gerven, J.M.A., van der Grond, J., de Vos, F., Moller, C., Rombouts, S., 2017b. Diminished posterior precuneus connectivity with the default mode network differentiates normal aging from Alzheimer's disease. Front. Aging Neurosci. 9, 97.
Klaassens, B.L., van Gorsel, H.C., Khalili-Mahani, N., van der Grond, J., Wyman, B.T., Whitcher, B., Rombouts, S.A., van Gerven, J.M., 2015. Single-dose serotonergic stimulation shows widespread effects on functional brain connectivity. Neuroimage 122, 440–450.
Kleinloog, D., Rombouts, S., Zoethout, R., Klumpers, L., Niesters, M., Khalili-Mahani, N., Dahan, A., van Gerven, J., 2015. Subjective effects of ethanol, morphine, delta(9)-tetrahydrocannabinol, and ketamine following a pharmacological challenge are related to functional brain connectivity. Brain Connect. 5 (10), 641–648.
Klumpers, L.E., Cole, D.M., Khalili-Mahani, N., Soeter, R.P., te Beek, E.T., Rombouts, S.A.R.B., van Gerven, J.M.A., 2012. Manipulating brain connectivity with δ(9)-tetrahydrocannabinol: a pharmacological resting state FMRI study. Neuroimage 63 (3), 1701–1711.
Kwong, W.H., Chan, W.Y., Lee, K.K.H., Fan, M., Yew, D.T., 2000. Neurotransmitters, neuropeptides and calcium binding proteins in developing human cerebellum: a review. Histochem. J. 32 (9), 521–534.
Laeng, B., Lag, T., Brennen, T., 2005. Reduced stroop interference for opponent colors may be due to input factors: evidence from individual differences and a neural network simulation. J. Exp. Psychol. Human. 31 (3), 438–452.
Lanctot, K.L., Herrmann, N., Yau, K.K., Khan, L.R., Liu, B.A., Loulou, M.M., Einarson, T.R., 2003. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. Can. Med. Assoc. J. 169 (6), 557–564.
Leonpacher, A.K., Peters, M.E., Drye, L.T., Makino, K.M., Newell, J.A., Devanand, D.P., Frangakis, C., Munro, C.A., Mintzer, J.E., Pollock, B.G., Rosenberg, P.B., Schneider, L.S., Shade, D.M., Weintraub, D., Yesavage, J., Lyketsos, C.G., Porsteinsson, A.P., Grp, C.R., 2016. Effects of citalopram on neuropsychiatric symptoms in Alzheimer's dementia: evidence from the CitAD Study. Am. J. Psychiatry 173 (5), 473–480.
Lezak, M.D., 2004. Neuropsychological Assessment. Oxford University Press, New York.
Li, B.J., Liu, L., Friston, K.J., Shen, H., Wang, L.B., Zeng, L.L., Hu, D.W., 2013. A treatment-resistant default mode subnetwork in major depression. Biol. Psychiatry 74 (1), 48–54.
Li, W., Antuono, P.G., Xie, C., Chen, G., Jones, J.L., Ward, B.D., Franczak, M.B., Goveas, J.S., Li, S.J., 2012. Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathway associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. Neuroimage 60 (2), 1083–1091.
Liem-Moolenaar, M., de Boer, P., Timmers, M., Schoemaker, R.C., van Hasselt, J.G.C., Schmidt, S., van Gerven, J.M.A., 2011. Pharmacokinetic-pharmacodynamic relationships of central nervous system effects of scopolamine in healthy subjects, Br. J. Clin. Pharmacol 71 (6), 886–898.
Lim, H.K., Juh, R., Pae, C.U., Lee, B.T., Yoo, S.S., Ryu, S.H., Kwak, K.R., Lee, C., Lee, C.U., 2008. Altered verbal working memory process in patients with Alzheimer's disease. Neuropsychobiology 57 (4), 181–187.
Lorenzi, M., Beltramello, A., Mercuri, N.B., Canu, E., Zoccatelli, G., Pizzini, F.B., Alessandrini, F., Cotelli, M., Rosini, S., Costardi, D., Caltagirone, C., Frisoni, G.B., 2011. Effect of memantine on resting state default mode network activity in Alzheimer's disease. Drugs Aging 28 (3), 205–217.
Mavroudis, I.A., Fotiou, D.F., Adipepe, L.F., Manani, M.G., Njau, S.D., Psaroulis, D., Costa, V.G., Baloyannis, S.J., 2010. Morphological changes of the human Purkinje cells and deposition of neuritic plaques and neurofibrillary tangles on the cerebellar cortex of Alzheimer's disease. Am. J. Alzheimers Dis. 25 (7), 585–591.
McCabe, C., Mishor, Z., 2011. Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. Neuroimage 57 (4), 1317–1323.
McCabe, C., Mishor, Z., Filippini, N., Cowen, P.J., Taylor, M.J., Harmer, C.J., 2011. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. Mol. Psychiatry 16 (6), 592–594.
McCance, I., Phillis, J.W., 1968. Cholinergic mechanisms in the cerebellar cortex. Int. J. Neuropharmacol. 7 (5), 447–462.
McCance, I., Phillis, J.W., Westerman, R.A., 1968. Acetylcholine-sensitivity of thalamic neurones: its relationship to synaptic transmission. Br. J. Pharmacol. 32 (3), 635–651.
McEntee, W.J., Crook, T.H., 1991. Serotonin, memory, and the aging brain. Psychopharmacology (Berlin) 103 (2), 143–149.
McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7 (3), 263–269.
Meltzer, C.C., Smith, G., DeKosky, S.T., Pollock, B.G., Mathis, C.A., Moore, R.Y., Kupfer, D.J., Reynolds, C.F., 1998. Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. Neuropsychopharmacology 18 (6), 407–430.
Mesulam, M.M., Geula, G., 1988. Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. J. Comp. Neurol. 275 (2), 216–240.
Mintun, M.A., LaRossa, G.N., Sheline, Y.I., Lee, S.Y., Dence, C.S., Robert, M.H., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C., 2005. Distribution of [^{11}C]PIB in a nondemented population: implication for use as an antecedent marker of Alzheimer's disease. Neuropsychopharmacology 30. S223-S223.

Mount, H.T.J., Dreyfus, C.F., Black, I.B., 1994. Muscarinic stimulation promotes cultured Purkinje-cell survival: a role for acetylcholine in cerebellar development. J. Neurochem. 63 (6), 2065–2073.
Mowla, A., 2009. Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia?: a double-blind clinical trial. Eur. Psychiatry 24 (5), 484–487.
Muir, J.L., 1997. Acetylcholine, aging, and Alzheimer's disease. Pharmacol. Biochem. Behav. 56 (4), 687–696.
Niesters, M., Khalili-Mahani, N., Martini, C., Aarts, L., van Gerven, J., van Buchem, M.A., Dahan, A., Rombouts, S., 2012. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. Anesthesiology 117 (4), 868–877.
Niesters, M., Sitsen, E., Oudejans, L., Vuyk, J., Aarts, L.P., Rombouts, S.A., de Rover, M., Khalili-Mahani, N., Dahan, A., 2014. Effect of deafferentation from spinal anesthesia on pain sensitivity and resting-state functional brain connectivity in healthy male volunteers. Brain Connect. 4 (6), 404–416.
Norris, H., 1971. The action of sedatives on brain stem oculomotor systems in man. Neuropharmacology 10 (21), 181–191.
Nyth, A.L., Gottfries, C.G., 1990. The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicenter study. Br. J. Psychiatry 157, 894–901.
Ownby, R.L., Crocco, E., Acevedo, A., John, V., Loewenstein, D., 2006. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch. Gen. Psychiatr. 63 (5), 530–538.
Palesi, F., Tournier, J.D., Calamante, F., Muhlert, N., Castellazzi, G., Chard, D., D'Angelo, E., Wheeler-Kingshott, C.A.M., 2015. Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. Brain Struct. Funct. 220 (6), 3369–3384.
Pepeu, G., Giovannini, M.G., 2009. Cholinesterase inhibitors and beyond. Curr. Alzheimer Res. 6 (2), 86–96.
Pesarin, F., 1990. On a nonparametric combination method for dependent permutation tests with applications. Psychother. Psychosom. 54 (2–3), 172–179.
Porsteinsson, A.P., Drye, L.T., Pollock, B.G., Devanand, D.P., Frangakis, C., Ismail, Z., Marano, C., Meinert, C.L., Mintzer, J.E., Munro, C.A., Pelton, G., Rabins, P.V., Rosenberg, P.B., Schneider, L.S., Shade, D.M., Weintraub, D., Yesavage, J., Lyketsos, C.G., Grp, C.R., 2014. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. J. Am. Med. Assoc. 311 (7), 682–691.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion (vol 59, pg 2142, 2012). Neuroimage 63 (2), 999-999.
Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2015a. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. Neuroimage 112, 278–287.
Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015b. ICA-AROMA: a robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277.
Repantis, D., Laisney, O., Heuser, I., 2010. Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: a systematic review. Pharmacol. Res. 61 (6), 473–481.
Richter-Levin, G., Segal, M., 1993. Age-related cognitive deficits in rats are associated with a combined loss of cholinergic and serotonergic functions. Ann. Ny. Acad. Sci. 695, 254–257.
Riekkinen, M., Tolonen, R., Riekkinen, P., 1994. Interaction between 5-HT_{1a} and nicotinic cholinergic receptors in the regulation of water maze navigation behavior. Brain Res. 649 (1–2), 174–180.
Rogers, M.A., Kasai, K., Koji, M., Fukuda, R., Iwanami, A., Nakagome, K., Fukuda, M., Kato, N., 2004. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. Neurosci. Res. 50 (1), 1–11.
Rombouts, S.A.R.B., Barkhof, F., Goekoop, R., Stam, C.J., Scheltens, P., 2005. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Hum. Brain Mapp. 26 (4), 231–239.
Sagud, M., Pivac, N., Muck-Seler, D., Jakovljevic, M., Mihaljevic-Peles, A., Korsic, M., 2002. Effects of sertraline treatment on plasma cortisol, prolactin and thyroid hormones in female depressed patients. Neuropsychobiology 45 (3), 139–143.
Samson, M., Claassen, D.O., 2017. Neurodegeneration and the cerebellum. Neurodegener. Dis. 17 (4–5), 155–165.
Schaefer, A., Burmann, I., Regenthal, R., Arelin, K., Barth, C., Pampel, A., Villringer, A., Margulies, D.S., Sacher, J., 2014. Serotonergic modulation of intrinsic functional connectivity. Curr. Biol. 24 (19), 2314–2318.
Schliebs, R., Arendt, T., 2011. The cholinergic system in aging and neuronal degeneration. Behav. Brain Res. 221 (2), 555–563.
Schmitt, J.A.J., Wingen, M., Ramaekers, J.G., Evers, E.A.T., Riedel, W.J., 2006. Serotonin and human cognitive performance. Curr. Pharmaceut. Des. 12 (20), 2473–2486.
Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D., 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron 62 (1), 42–52.
Seifritz, E., Baumann, P., Muller, M.J., Annen, O., Amey, M., Hemmeter, U., Hatzinger, M., Chardon, F., HolsboerTrachsler, E., 1996. Neuroendocrine effects of a 20-mg citalopram infusion in healthy males: a placebo-controlled evaluation of citalopram as 5-HT function probe. Neuropsychopharmacology 14 (4), 253–263.
Seo, Y., Shin, Y., Kim, H.S., Kang, I., Hong, I.S., Choi, S.W., Yu, K.R., Kang, K.S., 2014. Donepezil enhances Purkinje cell survival and alleviates motor dysfunction by inhibiting cholesterol synthesis in a murine model of Niemann Pick disease type C. J. Neuropathol. Exp. Neurol. 73 (3), 234–243.
Sheline, Y.I., Morris, J.C., Snyder, A.Z., Price, J.L., Yan, Z.Z., D'Angelo, G., Liu, C., Dixit, S., Benzinger, T., Fagan, A., Goate, A., Mintun, M.A., 2010. APOE4 allele disrupts resting state fMRI connectivity in the absence of amyloid plaques or decreased CSF Aβ42. J. Neurosci. 30 (50), 17035–17040.
Sheline, Y.I., Raichle, M.E., 2013. Resting state functional connectivity in preclinical Alzheimer's disease. Biol. Psychiatry 74 (5), 340–347.
Sheline, Y.I., West, T., Yarasheski, K., Swarm, R., Jasielec, M.S., Fisher, J.R., Ficker, W.D., Yan, P., Xiong, C.J., Frederiksen, C., Grzelak, M.V., Chott, R., Bateman, R.J., Morris, J.C., Mintun, M.A., Lee, J.M., Cirrito, J.R., 2014. An antidepressant decreases CSF Aβ production in healthy individuals and in transgenic AD mice. Sci. Transl. Med. 6 (236), 236re4.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155.
Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U.S.A. 106 (31), 13040–13045.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y.Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl. 1), S208–S219.
Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44 (1), 83–98.
Solé-Padullés, C., Bartres-Faz, D., Llado, A., Bosch, B., Pena-Gomez, C., Castellvi, M., Rami, L., Bargallo, N., Sanchez-Valle, R., Molinuevo, J.L., 2013. Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memory encoding in Alzheimer's disease. J. Clin. Psychopharmacol. 33 (2), 199–205.
Soreq, H., Seidman, S., 2001. Acetylcholinesterase - new roles for an old actor. Nat. Rev. Neurosci. 2 (4), 294–302.
Sperling, R.A., Dickerson, B.C., Pihlajamaki, M., Vannini, P., LaViolette, P.S., Vitolo, O.V., Hedden, T., Becker, J.A., Rentz, D.M., Selkoe, D.J., Johnson, K.A., 2010. Functional alterations in memory networks in early Alzheimer's disease. NeuroMolecular Med. 12 (1), 27–43.
Stroop, J.R., 1935. Studies of interference in serial verbal reactions. J. Exp. Psychol. 18, 643–662.
Sundermann, B., Beverborg, M.O.L., Pfleiderer, B., 2014. Toward literature-based feature selection for diagnostic classification: a meta-analysis of resting-state fMRI in depression. Front. Hum. Neurosci. 8, 692.
Tahmasian, M., Pasquini, L., Scherr, M., Meng, C., Forster, S., Bratec, S.M., Shi, K.Y., Yakushev, I., Schwaiger, M., Grimmer, T., Diehl-Schmid, J., Riedl, V., Sorg, C., Drzezga, A., 2015. The lower hippocampus global connectivity, the higher its local metabolism in Alzheimer disease. Neurology 84 (19), 1956–1963.
Thomann, P.A., Schlafer, C., Seidl, U., Dos Santos, V., Essig, M., Schroder, J., 2008. The cerebellum in mild cognitive impairment and Alzheimer's disease - a structural MRI study. J. Psychiatr. Res. 42 (14), 1198–1202.
Van de Ven, V., Wingen, M., Kuypers, K.P.C., Ramaekers, J.G., Formisano, E., 2013. Escitalopram decreases cross-regional functional connectivity within the default-mode network. PLoS One 8 (6), e68355.
Van Laar, M.W., van Willigenburg, A.P.P., Volkerts, E.R., 1995. Acute and subchronic effects of nefazodone and imipramine on highway driving, cognitive functions, and daytime sleepiness in healthy adult and elderly subjects. J. Clin. Psychopharmacol. 15 (1), 30–40.
Van Wingen, G.A., Tendolkar, I., Urner, M., van Marle, H.J., Denys, D., Verkes, R.J., Fernandez, G., 2014. Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest. Neuroimage 88, 47–53.
von Bardeleben, U., Steiger, A., Gerken, A., Holsboer, F., 1989. Effects of fluoxetine upon pharmacoendocrine and sleep-EEG parameters in normal controls. Int. Clin. Psychopharmacol. 4, 1–5.
Wechsler, D., 1981. The psychometric tradition: developing the Wechsler adult intelligence scale. Contemp. Educ. Psychol. 6 (2), 82–85.
Winkler, A.M., Ridgway, G.R., Douaud, G., Nichols, T.E., Smith, S.M., 2016a. Faster permutation inference in brain imaging. Neuroimage 141, 502–516.
Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92, 381–397.
Winkler, A.M., Webster, M.A., Brooks, J.C., Tracey, I., Smith, S.M., Nichols, T.E., 2016b. Non-parametric combination and related permutation tests for neuroimaging. Hum. Brain Mapp. 37, 1486–1511.
Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M., Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. Neuroimage 45 (Suppl. 1), S173–S186.
Zaidel, L., Allen, G., Cullum, C.M., Briggs, R.W., Hynan, L.S., Weiner, M.F., McColl, R., Gopinath, K.S., McDonald, E., Rubin, C.D., 2012. Donepezil effects on hippocampal and prefrontal functional connectivity in Alzheimer's disease: preliminary report. J. Alzheimer's Dis. 31 (Suppl. 3), S221–S226.
Zhang, S., Li, C.S.R., 2012. Functional connectivity mapping of the human precuneus by resting state fMRI. Neuroimage 59 (4), 3548–3562.