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CORTICAL BRAIN PERFUSION AND COGNITIVE EVENT RELATED POTENTIALS IN PATIENTS WITH PSYCHOMOTOR RETARDATION IN LATE ONSET DEPRESSION

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SUMMARY

Background: *Late onset depression is characterised by pronounced cognitive impairment, more somatic complaints and psychomotor retardation. Psychomotor slowing may be due to impairment in either motor or cognitive domain. Electrophysiology may be particularly convenient as a tool in studies of psychomotor retardation, as it can separate central cognitive processing from the motor processing.*

Subjects and methods: *In this study we compared event related potentials (ERP) in the two groups of patients with late onset depression and psychomotor slowing as measured by reaction time (RT): a group of patients with lower RT was compared to a group with a higher RT. Twenty patients with late onset depression were included in the study after they had reached remission. Four weeks after reaching remission patients were reevaluated clinically using Hamilton Depression Rating Scale, Mini Mental State Examination, and with a computer version of the Stroop task. ERP, accuracy and RTs were simultaneously recorded. Both groups of patients aditionaly underwent a perfusion SPECT imaging.*

Results: *There were no differences between the short and long RT groups of patients in amplitudes of the late positive Stroop related potentials. The group of patients with longer RTs showed significant hyperperfusion in precentral gyrus, parietal regions, cuneus and hypoperfusion within insular, frontal, temporal and limbic (parahyppocampal gyrus and anterior cingulate) cortices, as well as cerebellum.*

Conclusion: *We found no ERP differences between the two groups suggesting that although patients may differ on psychomotor retardation measured as RT, their cognitive abilities may be quite similar. Perfusion SPECT imaging however revealed a significant difference between them. This may be due to a process of compensation and applying different strategies to cope with cognitive impairment in the two groups.*

Key words: *cortical brain perfusion - psychomotor retardation - late onset depression*

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INTRODUCTION

Psychomotor retardation (PMR) is regarded as a key aspect of major depressive disorder (Schrjivers at al. 2008, Buyukdura et al. 2011). Patients with high lifetime psychomotor retardation factor scores are more likely to have longer duration of illness, suicide attempts, earlier age of onset, more depressive episodes, and higher indicators of bipolarity (Calugi et al. 2011).

Late onset depression differs from early onset depression: patients have more somatic complaints, they score worse on cognitive, particularly frontal functions tests, and many of them present with psychomotor slowness (Alexopoulos et al. 2002, Butters et al. 2004, Hammar et al. 2010). In geriatric depression psychomotor impairment is one of the main characteristics of the late onset depression, also known as "depression-executive dysfunction syndrome" (Lockwood et al. 2002, Morimoto & Alexopoulos 2013). In elderly untreated depressed patients, an additive effect of depression and aging on cognition and psychomotor retardation was found. Patients performed worse on clinical, cognitive and psychomotor measures (Beheydt at al. 2015).

Structural imaging studies suggest that patients with depression have frontostriatal abnormalities such as white matter changes in the basal ganglia and decreased volumes of the prefrontal cortex, caudate, and putamen. These deficits may be more profound in the presence of psychomotor retardation (Naismith et al. 2002, Steffens & Krishnan 1998).

A study with 99 m Tc-HMPAO single photon emission computed tomography (SPECT) found that in severe depression, severity of psychomotor retardation was negatively correlated with prefrontal, frontal and temporal perfusion (Mayberg et al. 1994, Narita et al. 2004). Hickie and colleagues found that the left neostriatum regional cerebral blood flow (rCBF) was inversely correlated with psychomotor retardation (Hickie et al. 2007).

Depressed elderly patients showed decreased rCBF in both left and right anterior frontal regions, more pronounced in the left hemisphere (Navarro et al. 2001, Cho et al. 2002). After 12 months remission the hypofrontality disappeared (Navarro et al. 2004). The depressive pseudodementia group showed decreased rCBF in the temporo-parietal regions, similar to that of Alzheimer 's patients group and different from the depression group free of cognitive impairment (Cho et al. 2002). Brain perfusion SPECT of treatment resistant depression compared to healthy group exhibited significant hypoperfusion within bilateral fronto-temporal, insular, and anterior cingulate cortices, as well as within the left caudate. Gender, age and type of mood disorder did not influence this hypoperfusion patterns (Richieri at al. 2015).

Relative to younger patients, geriatric depressed patients demonstrated increased glucose metabolism in a more extensive network of both anterior cortical regions, as well as posterior cortical regions (Smith et al. 2009). Studies in older depressed patient showed decreased anterior cortical and limbic metabolism and increases in posterior cortical regions and cerebellum with antidepressant treatment (Smith et al. 2002, Smith et al. 2009, Diaconescu et al. 2010). In younger depressed patients, antidepressant treatment increased anterior cortical metabolism and decreased metabolism in limbic areas. Regional differences in metabolic response to antidepressant medications between younger an older depressed patients may be attributable to differences in differential compensatory processes in the aging brain (Gunning & Smith 2011). Increased cortical metabolism was observed in geriatric patients relative to control subjects in areas that overlap to some extent with regions in which greater atrophy in patients are observed (Smith et al. 2009).

Functional neuroimaging studies in late-life depression reveal a pattern of abnormal activation of frontolimbic regions, generally characterized by hypoactivetion of specific dorsal cortical regions including dorsolateral prefrontal cortex (DLPFC) and the dorsal anterior cingulate cortex (ACC). In depressed elderly patients, relative to age-matched controls Aizenstein and collegues reported decreased DLPFC activation in addition to increased caudate activation in response to an explicit sequence learning test (Aizenstein et al. 2005). These initial task-based activation studies of late-life depression support emerging evidence from other clinical and cognitive techniques that cognitive control systems are disrupted in late life depression (Aizenstein et al. 2005, Alexopoulos et al. 2005).

Cognitive control is of particular interest in geriatric depression because of the vulnerability of cognitive control structures to aging (Vasic et al. 2009, Gunning-Dixon et al. 2009) and because specific cognitive control dysfunctions may explain a number of salient cognitive and other behavioral features of illness, including the inability to ignore irrelevant, especially negative, stimuli (Katz at al. 2010, Gunning & Smith 2011).

These changes may be detected also electrophysiologically. P300 is the most studied large positive event related potential (ERP) component that typically peaks at 300 ms after the onset of rare task relevant stimulus (Duncan et al. 2009). Once a unitary phenomenon, it is now believed to be composed of several parts that reflect an information processing cascade when attentional and memory mechanisms are engaged (Polich 2007). P300 might serve as a marker for decreased central processing in depressed subject (Bruder et al. 2009, Duncan et al. 2009).

Findings of abnormal P300 are less consistent in mood disorders and may be related to patients subtypes or to severity of depression (Kaustio et al. 2002). Patients with Alzheimer's dementia and patients with major depression and cognitive impairment had significantly longer P300 latency compared to depressed patients without cognitive impairment (Vandoolaeghe et al. 1998). Several ERP studies demonstrated P300 amplitude to be reduced in depressed patients (Gandagadhar et al. 1993, Anderer et al. 2002, Röschke & Wagner 2003, Urretavizcaya et al. 2003, Kawasaki et al. 2004), whereas some studies did not (Vandoolaeghe et al. 1998, Kaustio et al. 2002, Kaiser et al. 2003). The difference in findings across studies could be related to differences in patients' clinical features, with P300 reductions being more evident in patients diagnosed with melancholic depression (Urretavizcaya et al. 2003) and psychotic depression (Kaustio et al. 2002, Karaaslan et al. 2003).

The purpose of the present study was to compare cortical perfusion using perfusion SPECT and event related potentials between two groups of patients with psychomotor slowing in the symptoms free remission period: a group of patients with lower and higher reaction time (RT), respectively. We expected patients with longer RTs to have lower ERP amplitudes and frontal hypoperfusion on perfusion SPECT.

SUBJECTS AND METHODS

Subjects

Twenty patients (12 women and 8 men) with depression as defined by ICD 10 criteria were included in the study after they had reached remission. Depression started after the age of 60, which was taken as a cut-off for 'late onset' depression (Driscoll et al. 2005). Subjects were considered in remission if they no longer met the criteria for depression and had an Hamilton Depression rating Scale (HDRS) score below seven for four consecutive weeks (Hamilton 1960). Patients were compared to 20 age-, gender- and education-matched healthy controls.

We divided patients into a group with lower RT (1199 ms and below) and group with higher RT (1200 ms and over). Division between the two groups was decided according to the RT of healthy elderly individuals control group in the neutral condition of the Stroop task, namely three standard deviations above average RT for the control group (1200 ms).

Table 1. Demographic and clinical characteristics of two groups of patients with different psychomotor retardation and healthy controls

Characteristic	Controls	RT < 1200 ms	RT > 1200 ms	p value
N (male: female)	8:12	4:8	4:4	
Age (mean, S.D.)	72.8 (6)	71.6 (4.5)	74.3 (4.8)	0.23
Education (years, mean, S.D.)	8.9 (2.7)	8.17 (2.62)	7.0 (1.51)	0.34
HDRS[2] (21 - item) (mean, S.D.)		29.58 (7.04)	28.5 (5.43)	0.72
HDRS[2] remission (mean, S.D.)	2.0 (1.8)	5.83 (1.47)	6.13 (1.13)	0.77
Reaction time (ms, mean, S.D.)	877 (106)	1016 (96)	1374 (19)	0.00003
MMSE[1] (mean, S.D.)	29.4 (0.6)	28.4 (1.31)	28.0 (0.76)	0.23

[1] MMSE - Mini Mental State Examination; [2] HDRS - Hamilton Depression Rating Scale

Subjects were excluded if they had history or signs of (i) another psychiatric disorder, (ii) medical illness, nonpsychotropic medication or physical disability that may affect cognition, (iii) alcohol or drug abuse or dependence, (iv) clinically diagnosed central neurological disorder.

All patients in the study were followed by a geriatric psychiatrist. Participants were initially prescribed a selective serotonin reuptake inhibitor (SSRI). If treatment with an SSRI did not produce sufficient response, the next option was to change treatment to venlafaxine or combinations of antidepressants. Further options included tryciclic antidepressants or lithium augmentation. In the current sample, patient received: sertraline, 9; paroxetine, 4; citalopram, 5; venlafaxine,1; maprotiline, 1. Any anxiolytics (including benzodiazepines) and hypnotics (except zolpidem) were disallowed within the last week prior testing. Patients and controls suffering from any medical condition that might affect fine motor or cognitive processes were excluded. None of the healthy controls received any psychiatric medications. All subjects had Mini Mental State Examination (MMSE) (Folstein et al. 1975) score of 27 or above and none was considered demented according to ICD-10 criteria (Table 1).

Procedure

Patients were recruited from the Out- and In-patient service of a Psychiatric Hospital in western Slovenia. Psychiatric diagnosis was obtained according to ICD-10 criteria using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990). A structured interview was performed to confirm the diagnosis and a structured interview used to rule out other psychiatric disorders. A 17-item Hamilton depression rating scale - HDRS (Hamilton 1960, Mulsant et al. 1994) was additionally used in the evaluation. The appropriate antidepressant treatment was introduced. Perfusion SPECT has been performed 4 weeks after reaching the remission, together with HDRS, MMSE (Folstein et al. 1975), computer version of the Stroop test (Repovš 2004) and EEG.

Hypotheses were tested by analyzing and comparing the results between the studied groups.

The study was approved by the Ethics Committee of Slovenia, and all the subjects signed informed consent prior to participation in the study.

Instruments

Computer version of the Stroop color word naming task

Each participant completed one session of a single-item computer version Stroop color-word task in which different stimuli were individually presented on the screen while the participants named the color in which the stimulus was presented or read the word that was presented (Stroop 1935, Golden 1978). Five types of stimuli were used in the task: a) neutral stimuli, b) verbal stimuli (three regular Slovene words matched in frequency and length to target color words but without color meaning or conotation), c) congruent stimuli, d) incongruent stimuli, and e) word reading stimuli (Repovš 2004).

Each trial started with a variable length delay of 2.2, 2.4 or 2.6 seconds, after which the target stimulus was presented. Subject responded verbally by saying the response aloud. The reaction times of the response were captured by concurrent recording using a microphone, while accuracy was recorded by the experimenter. Subjects were instructed to respond as soon as possible while still being sure in their responses.

Each participant first completed a training block of 18 randomly presented nonword neutral trials, then another training block of 15 randomly selected trials, this time employing all the possible types of stimuli to get familiar with the task. Participants then completed 12 task blocks of 45 trials each in which each of five different types of stimuli was presented 9 times in a quasi-random sequence in which no color and no stimulus type was presented twice in a row. Only accurate trials were further analysed.

RT recording

RT was defined as the time between presentation of the stimulus and the onset of the recorded verbal response. The stimulus marker and voice recording were co-registered with the EEG signal on separate signal channels. Voice was recorded using a microphone pla-

ced in front of the subject and attached to the EEG preamplifier. The RTs for each trial were extracted semi-automatically using custom made software written in Matlab (MathWorks, Natick, Massachusetts). Specifically, the algorithm searched for and marked significant amplitude changes in the recorded voice signal.

EEG recording

EEG activity was recorded simultaneously with the Stroop task, using Ag/AgCl electrodes attached at Fz, Cz and Pz sites (employing the international EEG 10 – 20 system), referenced to linked electrodes placed on the left and right earlobes; the ground electrode was fixed to the temple. Electrooculographic (EOG) activity was recorded bipolarly with electrodes attached 2 cm laterally and 2 cm above the right eye. The recordings were amplified by factor 60 000, 1-100 Hz filters were used, and individual resistance did not exceed 5 kOhm. For every trial 2048 samples were recorded with 1 kHz sampling frequency, starting at 83 ms interval before presentation of the stimulus. The EEG signal was recorded using Nicolet SM 2000 and all the following analyses were performed using custom software written in Matlab.

To control for eye movement and blink artefacts, the EOG signal recorded concurrently with EEG was subtracted out from the EEG signal by the use of linear regresion across all the trials for each of the 3 EEG channels separately. The procedure was performed for each subject independently.

Analysis of waveforms

ERPs were averaged separately according to condition in each of the five conditions. ERP peaks were identified in the channels in which they were most prominent, and the latency of these peaks was measured with respect to the stimulus onset. The amplitudes of these peaks were measured as the average of the amplitudes at the peak value used for the latency measurements. Amplitudes were measured with respect to the prestimulus baseline. Peaks were named according to their polarity (N = negative, P = positive), and latency.

The N100 was defined as the largest negativity in the latency window 50-150 ms; the largest positivity following the N100 was defined as the P200 wave. The N200 wave was defined as the largest negativity following the P200 wave. The P300 component was defined as the largest positive peak occurring at all electrode sites following the N100-P200-N200 complex within latency window between 350 and 700 ms with P300a and P300b having central and parietal maximum, respectively.

Statistical analysis

Statistical analysis of the data was performed using R Statistic Package. To test for general differences in RTs a two-way condition (neutral, verbal, congruent, incongruent and word reading) by group (patients vs. controls) analysis of variance (ANOVA) was computed.

To further investigate the differences in the response times obtained in the control and depressed patient groups, the RTs were translated to individual estimates of Stroop interference and facilitation effects; the possible differences between them were then tested for using the two-tailed *t*-test for independent samples.

For the ERP analysis recordings were further filtered by 30 Hz low pass digital filter. EOG activity at each recording was individually substracted from each channel using the regression method. Individual ERP averages were used as the basis for presenting the grand averages and the computation of running the *t*-test.

Perfusion SPECT imaging

Upon acceptance to Department of Nuclear Medicine at University Medical Centre Ljubljana all study participants were placed to rest in a quiet dimly lit room with eyes closed for 30 minutes. 99 mTc-bicizat (99m Tc-ECD) with activity 600 MBq was intravenously administered to the participants, and they were left to rest for another 20 minutes. SPECT imaging was performed using dual-head Siemens MultiSPECT scanner equipped with parallel-hole, low-energy, high-resolution collimator in 120 angles through 360 degrees in step-and-shoot mode. Image reconstruction was performed using filtered back-projection reconstruction algorithm into a 128 x 128 matrix with a voxel size 3,9 X 3,9 X 3,9 mm^3.

Perfusion SPECT image analyses

Perfusion SPECT brain images were converted to Analyze format using MRIcro software (http://www.cabiatl.com/mricro/mricro/mricro.html). Then they were spatially normalized into a standard Montreal Neurological Institute (MNI) based SPECT template and smoothed using a Gaussian kernel of 12x12x12 mm FWHM, both using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/SPM8/), running in Matlab R2014a (MathWorks Inc., Natick, MA).

Two sample t-test was performed to compare perfusion SPECT brain scans between a group of subjects with RT > 1200 ms and a group of subjects with RT < 1200 ms, where RT was individual subject's result in Stroop test. Perfusion in brain regions was reported as significantly different between the two groups at threshold level $p<0.01$, and cluster extent threshold 100.

RESULTS

ERP results: Differences in amplitudes of the late positive Stroop related potentials

There were no differences between the short and long RT groups of patients with late onset depression during remission period in N100, P200, N200, P300a latencies and in amplitudes of the late positive Stroop related potentials in the period of about 500-600 ms period for the neutral condition ($p=0.83$) (Figure 1), verbal condition ($p=0.24$), incongruent condition ($p=0.93$), congruent condition ($p=0.78$), reading ($p=0.30$).

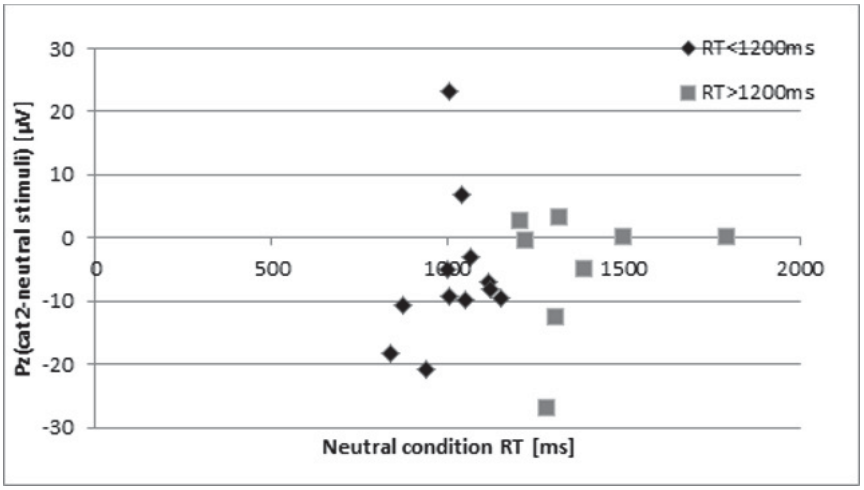

Figure 1. Differences in amplitudes of the late positive Stroop related potentials (neutral condition) between the group of patients with lower RT (RT < 1200ms) and group with higher RT (RT > 1200ms)

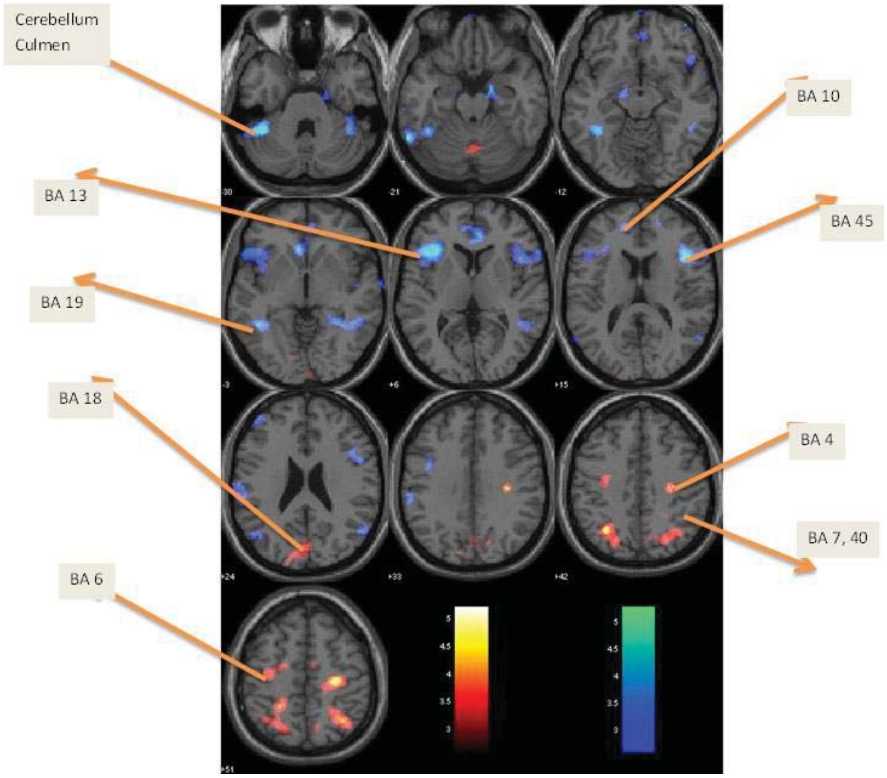

Figure 2. Brain perfusion SPECT: Comparison of the regional cerebral blood flow between late onset depression patients with short vs. long RT. Blue colour shows areas where the slower group exhibits decreased brain cerebral blood flow (hypoperfusion) in comparison with the faster one, whereas red colour marks the areas where the slower group exhibits increased brain cerebral blood flow (hyperperfusion) in comparison with the other group. (BA – Brodmann area). Perfusion in brain regions was reported as significantly different between the two groups at threshold level $p<0.01$, and cluster extent threshold 100

Results of perfusion SPECT image comparison

The group of patients with longer RT (> 1200ms) showed significant hyperperfusion of precentral gyrus, parietal region (superior and inferior lobule, precuneus), cuneus and hypoperfusion within insular, frontal, temporal, lymbic (parahyppocampal gyrus) and anterior cingulate cortices, as well as cerebellum (Table 2, Figure 2).

DISCUSSION

The present study compared two groups of patients with higher and lower PMR and, as a key finding found no differences in cognitive ERPs but statistically important differences in brain perfusion of several areas. Neuropsychological profile of depression in older people is typically described as being 'frontosubcortical'

Table 2. Results of perfusion SPECT brain image comparison between groups at threshold p<0.01 on cluster level: Comparison between late onset depression patients with short vs. long RT (Ke – size of cluster, BA – Brodmann area)

Ke	Area	BA
Hyperperfusion		
6862	right frontal lobe – precentral gyrus left superior parietal lobul	6, 4, 7
1491	right inferior parietal lobul precuneus cuneus	40, 7, 18
Hypoperfusion		
942	cerebellum – culmen left tempral, left limbyc – parahippocampal gyrus	37, 19
1023	left sub-lobar – insula left frontal - inferior frontal gyrus	13, 47
868	right frontal – inferior frontal gyrus	45, 9
624	left frontal – medial frontal gyrus left and right limbic lobe – anterior cingulate	10, 24

including key fronto-striatal and limbic circuitry (Butters et al. 2004, Elderkin-Thompson et al. 2007). While somewhat heterogeneous, impairments are typically found in the domains of executive functioning, processing speed, learning and memory (Naismith et al. 2012, Jayaweera et al. 2016). Psychomotor retardation is one of the main characteristics of the late onset depression which includes motor and cognitive impairments (Beheydt et al. 2015). Retardation modifies all the actions of the individual, including motility, mental activity, and speech (Buyukdura et al. 2011, Benabi et al 2013).

Cognitive and motor component of psychomotor retardation can also be assessed and quantified with neuropsychological testing.

Reaction time methods have been used as a simple and objective index of PMR. Depressed subjects are slower than normal controls in simple and choice RT tasks (Bieliauskas & Lamberty 1995, Azorin et al. 1995). However it is not clear whether depression affects all stages of information-processing or only some of them. RT data from the two-choice visual RT task suggest that depression spares the stage of stimulus preprocessing, but affects the stage of motor adjustment (Bonin-Guillaume et al. 2004). Numerous studies have also demonstrated the independence of central (cognitive) and peripheral (motor) components of reaction time by separately measuring the time required to initiate a response (decision time) and the time required to carry out the motor activity to complete the response (Benabi et al. 2013).

Electrophysiology may be particularly convenient as a tool in studies of PMR, as it can separate central cognitive processing from the motor processing (Duncan et al. 2009). Several ERP studies demonstrated P300 amplitude to be reduced in depressed patients (Röschke & Wagner 2003, Urretavizcaya et al. 2003, Kawasaki et al. 2004).

In a previous study we compared patients with late onset depression and group of healthy controls (Pišljar et al. 2013). The study of cognition was focused on executive function and speed of information processing. It was measured with Stroop-related ERPs and RTs in a modified computer version of the Stroop test which is highly sensitive to frontal functions. RTs were significantly prolonged in patients in all conditions of the Stroop paradigm, and the interference effect was significantly greater in patients compared to controls. Results also revealed abnormal late positive Stroop related potentials in the period of about 500-600 ms period corresponding to the so-called P300b wave. Our study supports the view that patients with late onset depression are also cognitively impaired and that this impairment persists in the period of early remission. Using more sensitive ERP measurement of the frontally oriented Stroop task, we demonstrated impaired information processing at an earlier, pre-response related stage (Pišljar et al. 2013).

We wondered whether abnormal ERPs as a marker of worse cognitive functioning in late onset depression, correlate with severity of PMR. Therefore we measured Stroop-related ERPs in depressed patients in remission and compared results of the group with longer RTs with results of the group with shorter RTs. No ERP differences between the two groups were found supporting the view that patients with greater PMR in late onset depression may not necessarily be cognitively more impaired. This finding is relevant for planning cognitive rehabilitation as patients with late onset depression and PMR may retain ability for improvement of cognitive functioning.

To elucidate possible mechanisms of PMR we studied also brain perfusion in elderly depressed patients who had similar cognitive impairment but differed in the degree of PMR. The group of patients with longer RTs showed significant hyperperfusion of precentral gyrus, parietal regions (superior and inferior lobule, precuneus), cuneus and hypoperfusion within insular, frontal, temporal, limbic (parahyppocampal gyrus and anterior cingulate) cortices, as well as cerebellum. Depressed patients with longer RTs (i.e. greater PMR)

exhibited hypoperfusion in deep brain structures associated with mood and drive and significant hyperperfusion of higher cortical structure. This may be due to a process of compensation, similarly to findings of Smith and colleagues who reported increased cortical glucose metabolism in geriatric depressed patients relative to the demographically matched controls in anterior (right and left superior frontal gyrus) and posterior (precuneus, inferior parietal lobule) cortical region, particularly in brain regions in which cerebral atrophy was observed and postulated such finding to be due to a compensatory mechanism (Smith et al. 2009). Specific locations may reflect age-related vulnerability of some of the brain systems implicated in mood disorders (e.g., cognitive control system) (Gunning & Smith 2011), such as the cuneus that - in addition to its traditional role as a site for basic visual processing - is associated with better inhibitory control in bipolar depression patients (Haldane et al. 2008).

CONCLUSIONS

Patients with geriatric depression in early remission have abnormal premotor processing when compared to healthy controls. Using more sensitive ERP measurement of the frontally oriented Stroop task, it was demonstrated that they are impaired in early cognitive and stimulus evaluation impairment as well as in the motor stage.

Patients with geriatric depression in early remission have similar cognitive impairment but may differ on the degree of PMR. Those with greater PMR exhibited hypoperfusion in deep brain structure and significant hyperperfusion of higher cortical structure when compared to those with lower PMR, possibly reflecting different strategies to cope with cognitive impairment.

Limitations

Our results should be considered in the light of several limitations such as relatively small sample size, naturalistic treatment and the methods. A larger sample size would have been desirable. Only severly depressed elderly patients were included in our sample, meaning that the results cannot be extrapolated to the general population. Perfusion SPECT is less sensitive then fluorodeoxyglucose possitron emission tomography (FDG PET), which would be better to detect even smaller brain activity changes, however FDG PET was not available when the study was performed.

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Conflict of interest: None to declare.

Contribution of individual authors:

Marko Pišljar, Maja Trošt & Zvezdan Pirtošek have contributed to the concept of the study, interpretation of data and manuscript preparation. Grega Repovš participated in the design of study and data interpretation.

Petra Tomše was involved in statistical analyses and interpretation of data.

All authors approval of the version to be published.

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