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Research Letter

Reproducibility and predictive value of the post-imperative negative variation during aversive instrumental learning in depression

Previous studies have shown that loss of control during instrumental learning induces extensive response-outcome uncertainty, accompanied by enhanced mid-frontal post-imperative negative variation (PINV) in multi-channel electroencephalography (EEG; Rockstroh *et al*. 1979; Elbert *et al*. 1982; Kathmann *et al*. 1990; Diener *et al*. 2009*a*, *b*). A recent standardized low-resolution brain electromagnetic tomography study (known as sLORETA) suggests involvement of the anterior cingulate cortex in the detection of response conflict during loss of control and PINV generation (Diener *et al*. 2010).

In healthy individuals, control over aversive stimulation prior to loss of control normalizes PINV magnitudes during restitution of control, which has been attributed to immunization (Diener *et al*. 2009*b*). In a previous EEG study employing a forewarned reaction paradigm (S1-S2) with varying stressor controllability, we investigated physiological effects of stressor uncontrollability and their cognitive correlates in depressed and healthy individuals (Diener *et al*. 2009*a*). Compared with healthy individuals, depressed participants showed enhanced frontal PINV magnitudes during both loss and restitution of control. In addition, enhanced PINV during restitution of control was linked to habitual rumination in the patients. However, information on the robustness and predictive value for the course of depression of these findings is lacking.

The aims of the present study were to investigate whether differences in frontal PINV magnitudes between depressed patients and controls, as identified at baseline (T1) during various levels of controllability (Diener *et al*. 2009*a*), were reproducible in a follow-up assessment taking place 6 months after baseline (T2), and to assess whether frontal PINV magnitudes, measured at T1, could predict depressive symptom levels and diagnostic status at T2. Together, these research questions address the role of enhanced frontal PINV during aversive instrumental learning as a possible state or trait marker for depression.

Follow-up subjects were 39 participants from the Diener *et al*. (2009*a*) study (78% of the original cohort). Of these, 32 subjects (17 patients, 15 controls) provided valid EEG data at T2, where the experimental paradigm from T1 was reapplied. A full description of the instrumental conditioning paradigm is given by Diener *et al*. (2009*a*). Briefly, unmedicated depressed individuals, who fulfilled criteria for major depressive disorder (MDD) and/or dysthymic disorder according to DSM-IV (APA, 1994), and age- and sex-matched healthy controls were tested in an expanded forewarned reaction paradigm. The S1-S2 reaction paradigm consisted of a warning stimulus (S1, 600 Hz/60 db tone of 4 s duration) followed by an imperative stimulus (S2, 1000 Hz/60 db tone of 1 s duration). Subjects were instructed to respond to S2 by pressing the correct (left or right) button to avoid aversive electric stimulation. Stressor controllability (aversive e-shock) varied across three consecutive conditions of 40 trials each: (*a*) initial control (IC); (*b*) loss of control (LC); (*c*) restitution of control (RC). During IC and RC, but not during LC, subjects could learn to avoid the aversive stimulation by pressing the correct button immediately after the start of S2. During the experiment, reaction times, errors, ratings of controllability, arousal, emotional valence and helplessness were assessed together with the PINV at frontal, central and parietal recording sites. PINV magnitudes were defined as mean activity (μV) during a segment between 800 ms and 3500 ms following S2 termination relative to a 1000 ms pre-trial baseline (see Diener *et al*. 2009*a*). As at T1, valid EEG epochs (i.e. voltage step/sampling point $<50\,\mu$V, amplitude $\leqslant 100\,\mu$V and $\geqslant -100\,\mu$V) did not differ for group [$F(1,30)=0.008$, $p=0.93$], condition [$F(2,29)=0.115$, $p=0.89$] or group × condition [$F(2,29)=0.426$, $p=0.66$]. For this brief report, we focus on PINV data at the midline frontal recording site (Fz), because these had differentiated significantly between depressed subjects and controls during LC and RC at T1. Habitual rumination was assessed with the German version of the Response Styles Questionnaire (see Huffziger *et al*. 2009), and depressive symptoms with the Beck Depression Inventory-II (BDI-II; Beck *et al*. 1996).

At T2, the depressed sample consisted of 17 individuals [eight men and nine women aged 29–61 years, mean age 47.7 (S.D. = 8.3) years] who had fulfilled diagnostic criteria for MDD ($n=11$) or dysthymia ($n=6$) at T1. Of these, seven individuals (five MDD and two dysthymia) did not fulfil criteria for MDD and/or

dysthymia at T2, i.e. were considered remitted during the T1–T2 interval. To increase statistical power, we included both remitted and non-remitted patients at T2 in the present analyses. Seven patients were in psychotherapy at T2, of which four additionally received antidepressant medication. The healthy control sample at follow-up included 15 individuals [six men, nine women aged 30–60 years, mean age 44.9 (S.D. = 8.3) years]. Importantly, depressed and healthy individuals who participated in T2 did not differ from those who had dropped out regarding any baseline variables inspected in the following analyses (all $p > 0.20$).

The depressed group at T1 still displayed substantially higher depression scores at T2 [17.8 (S.D. = 12.2)] than controls [1.5 (S.D. = 2.1)] [$F(1,30) = 26.00$, $p < 0.001$]. Comparable to T1, subjective controllability ratings at T2 mirrored the controllability levels of the experimental design by showing a significant decrease from IC [51.13 (S.D. = 36.82)] to LC [34.19 (S.D. = 34.06)] [$F(1,29) = 8.73$, $p = 0.006$], and a significant increase from LC to RC [48.71 (S.D. = 38.45)] [$F(1,29) = 10.91$, $p = 0.003$], while group differences were non-significant (interactions time × group, all $p > 0.20$). Helplessness ratings increased significantly from IC [18.39 (S.D. = 22.34)] to LC [25.48 (S.D. = 29.25)] [$F(1,29) = 4.60$, $p = 0.041$] and decreased non-significantly from LC to RC [20.16 (S.D. = 22.86)] [$F(1,29) = 2.19$, $p = 0.150$] with non-significant group differences (all $p > 0.20$). Similarly, errors and reaction times across different conditions differed non-significantly between groups (all $p > 0.10$).

Patients and controls did not differ significantly with respect to frontal PINV during IC [−0.79 (S.D. = 3.53) *v.* −0.10 (S.D. = 1.84)] [$F(1,30) = 0.46$, N.S.] and LC [−3.59 (S.D. = 5.65) *v.* −2.2 (S.D. = 1.30)] [$F(1,30) = 0.85$, N.S.] at T2. However, patients displayed significantly larger PINVs during RC [−3.02 (S.D. = 3.88) *v.* −0.63 (S.D. = 1.31)] [$F(1,30) = 5.17$, $p = 0.03$]. Separate pairwise comparisons revealed that both patients [$t(16) = 3.01$, $p = 0.008$] and controls [$t(14) = 3.93$, $p = 0.004$] showed a significant increase in frontal PINV from IC to LC. In contrast, PINV decreased significantly again in controls [$t(14) = -3.38$, $p = 0.004$] but not in patients [$t(16) = -0.68$, N.S.] during RC. As at T1, larger PINVs during LC ($r = -0.414$, $p = 0.049$) and during RC at T2 ($r = -0.457$, $p = 0.033$) were linked to higher BDI-II depression scores in the patient sample, while respective coefficients were negligible in the control sample (all $p > 0.10$). Importantly, group differences in PINVs during RC diminished when BDI-II scores at T2 were entered as a covariate into the respective analysis of covariance model [group: $F(1,30) = 0.00$, N.S, BDI-II score: $F(1,31) = 7.13$, $p = 0.012$].

In a next step, we regressed BDI-II scores at T2 on BDI-II depression scores at T1 (forced into the model in a first block to elucidate net effects of the other predictors), and on mid-frontal PINV during IC, LC and RC, and symptom- and self-focused rumination at T1 (stepwise selection in a second block), separately for the two groups. When adjusting for BDI-II scores at T1, only symptom-focused rumination at T1 predicted depressive symptoms at T2 in patients [$\beta = 0.506$, $t(16) = 2.29$, $p = 0.037$] and marginally significantly in controls [$\beta = 0.334$, $t(14) = 1.97$, $p = 0.065$], while PINV magnitudes failed to reach statistical significance (all $p > 0.70$). A further multiple regression, which additionally controlled for treatment status of patients at follow-up (medication, psychotherapy, or both) revealed identical results. Finally, a logistic regression analysis with the total sample that included the same predictors showed that symptom-focused rumination significantly predicted diagnostic status (MDD and/or dysthymia) at follow-up [$\beta = 0.555$, S.E. = 0.26, Wald (1) = 4.55, $p = 0.033$], while all other predictors were non-significant (all $p > 0.10$).

This follow-up study replicated earlier baseline findings (Diener *et al*. 2009*a*), indicating that depressed individuals show characteristic alterations in frontal responsivity as indexed by the PINV during aversive instrumental learning, particularly during restitution of control. Enhanced PINV magnitudes during loss of control in depressed and healthy individuals have been attributed to the engagement of frontal areas to resolve task ambiguity in a situation where learned response-outcome contingencies are disrupted (Diener *et al*. 2009*a*, *b*). However, while PINV magnitudes decrease again in healthy subjects during restitution of control, depressed individuals continue to show enhanced mid-frontal PINV magnitudes. Therefore, although exhibiting similar subjective controllability, error rates and reaction times, depressed individuals appear to need enhanced prefrontal activation to compensate for effects of previously induced task ambiguity when control is objectively re-established. This bias appears to be relatively robust, because it was identified at two measurements over a 6-month interval. Comparable to T1, PINV magnitudes during restitution of control at T2 were related to concurrent depression levels in the patient sample, and when controlling for concurrent BDI-II scores, the group difference in frontal PINV diminished. Therefore, it may be concluded that the PINV magnitudes wax and wane in parallel to the severity of depressed symptomatology. Together with the observation that frontal PINV at T1 did not predict depressive symptom levels or diagnostic status at T2 when baseline symptom levels were controlled, these results indicate that enhanced PINV during restitution of control in depressed individuals represents a state rather than a trait marker for depression. Therefore, it

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may be regarded as an indicator of altered neuroplasticity in depression, reflecting prolonged susceptibility of depressed individuals towards uncontrollable stress. This process can apparently be reversed in the context of clinical improvement.

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Declaration of Interest

None.

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Letter to the Editor

Migrant status, vitamin D and risk of schizophrenia

Bourque and colleagues have provided a useful update of the evidence linking migrant status and risk of schizophrenia (Bourque *et al*. 2010). The evidence is convincing. What remains for the research community is to generate biologically plausible mechanisms that may underpin this increased risk. Previously, we proposed that low prenatal vitamin D might be a risk factor contributing to the increased risk of schizophrenia in certain migrant groups (McGrath, 1999). Bourque *et al*. note in their review that this hypothesis might account for part of the increased risk, but suggest that this candidate 'could scarcely account for the higher risk among lighter-skinned immigrants in some contexts (e.g. Moroccans in The Netherlands) or other groups who moved to warmer climates'.

In fact, there is abundant evidence showing that 'lighter-skinned immigrants' such as the Moroccans in the Netherlands are at increased risk of hypovitaminosis D. A detailed systematic review has recently been published on this topic (van der Meer *et al*. 2010). With respect to the relative difference in this exposure between different migrant groups, a population-based study of German children and adolescents ($n = 10\,015$) has provided informative relative risks (Hintzpeter *et al*. 2008). Compared with non-immigrants, those from Africa have the highest adjusted odds ratio for vitamin D deficiency (about seven-fold), followed by migrants from Arab-Islamic countries (about six-fold) and Turkey (about four-fold) (Hintzpeter *et al*. 2008). Apart from darker skin colour, variables related to dress (e.g. wearing a veil), behaviour (e.g. less outdoor activities) and diet also contribute to an increased risk of vitamin D deficiency in certain minority groups, regardless of skin colour or ethnicity (Rejnmark *et al*. 2004; Holick, 2007; Lips, 2010). Of course, you do not need to be a migrant to have low vitamin D deficiency and insufficiency are prevalent in many nations (Mithal *et al*. 2009).

The original vitamin D hypothesis focused exclusively on prenatal exposures. Animal experiments