www.nature.com/npp

Neuropsychopharmacology

ARTICLE

Effects of clonidine on MMN and P3a amplitude in schizophrenia patients on stable medication

Caitlyn Kruiper[1,2], Birte Y. Glenthøj[1,3] and Bob Oranje[1,2,3]

Schizophrenia is a complex brain disease involving several neurotransmitter systems, including aberrant noradrenergic activity, which might underlie cognitive deficits. Clonidine is an α_{2A}-agonist and previous research has demonstrated that single dosages of clonidine normalize sensori(motor) gating in schizophrenia. Currently, we investigated whether clonidine is able to normalize mismatch negativity (MMN) and P3a amplitude deficits in this same group of patients. This is important, since reports have shown that MMN amplitude is associated with cognitive functioning and daily life functions in schizophrenia. Twenty chronically ill, male schizophrenia patients were tested with the MMN paradigm from the Copenhagen Psychophysiological Test Battery (CPTB) on 5 occasions, separated by a week. Patients received randomized, yet balanced, either a placebo or a single dose (25, 50, 75 or 150 µg) of clonidine (each dose only once) on top of their usual medication on each occasion. Patients were matched on age and gender with 20 healthy controls (HC) who did not receive any treatment. We found decreased MMN and P3a amplitudes in our patients compared to HC. Although clonidine did neither significantly increase MMN nor P3a amplitude in our patients, it did increase certain levels of MMN and P3a amplitude such that these were not significantly different anymore from the healthy controls. Together with our previous reports indicating normalized sensori(motor) gating in the same patients following administration of clonidine, our results could be of potential high clinical relevance in treating schizophrenia. Future studies should focus on longer trial periods to investigate if clonidine also improves cognitive functioning in schizophrenia.

Neuropsychopharmacology (2019) 44:1062–1067; https://doi.org/10.1038/s41386-019-0351-6

INTRODUCTION

Schizophrenia is a severe brain disorder with profound deficits in prefrontal cortical cognitive functioning. Despite cognitive deficits being considered a core feature in schizophrenia [1], current medical treatment is still mainly focused on the reduction of positive symptoms by reducing the dopamine D2 and/or the combined D2 and serotonin (5-HT2A) receptor systems by means of antipsychotics. However, when the initial psychotic symptoms are relieved, cognitive symptoms remain and are associated with functional impairment [2, 3]. In the past two decades, research has focused on targeting cognitive deficits by pharmacological intervention; however, so far this effort has been proven to be clinically challenging.

One of the key neurotransmitters involved in cognition is noradrenaline (NA). From the locus coeruleus (LC), noradrenergic neurons project into the prefrontal cortex (PFC), where attention and working memory are modulated by NA (for an extensive review on the role of noradrenaline in cognition, see Borodovitsyna et al. [4]). NA facilitates cognitive functions by engagement of α2 receptors, more specifically $\alpha2_a$ receptors. These receptors are presynaptically located in the LC and when activated, noradrenergic transmission to the PFC is reduced. In contrast, in the PFC the $\alpha2_a$ receptors are located postsynaptically and extensive evidence exists that activation of these receptors are beneficial to cognitive functions [5]. It is important to note that α2 receptors have a lower threshold for activation by NA than α1 receptors, which need higher levels (e.g., during stress) of NA to be activated and long-term activation of α1 receptors has a detrimental effect on cognitive functioning [6–8]. Indeed, a number of studies report on increased noradrenergic transmission in schizophrenia [6, 9, 10], which might be the cause of the many cognitive dysfunctions that are usually reported in this disorder [5, 11, 12]. Extensive evidence exists that selective α2-agonists, such as clonidine, could restore the imbalance in α1 and α2 activity in the PFC, by simultaneously reducing NA levels by activating the presynaptic $\alpha2_a$ receptors in the LC, as well as activating postsynaptic $\alpha2_a$ receptors in the PFC [9, 10, 13]. Theoretically therefore, these agonists should improve cognition in schizophrenia patients.

Mismatch negativity (MMN) is believed to reflect an automated response to a change in a repetitive (ongoing) sequence of auditory stimuli [14]. The brain's response to this change can be recorded with electroencephalography (EEG). MMN normally peaks between 100 and 200 ms after onset of the deviant sound, depending on the specifics of the paradigm used, and is usually expressed as the difference wave derived by subtracting an individual's EEG response to the standard sound from his/her response to the deviant sound [14]. Two different generators of the MMN response have been identified: a temporal generator which is associated with sensory memory and a frontal generator

[1]Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Center Glostrup, University of Copenhagen, Copenhagen, Denmark; [2]Department of Psychiatry, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands and [3]Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
Correspondence: Caitlyn Kruiper (c.kruiper-2@umcutrecht.nl)

Received: 11 October 2018 Revised: 13 February 2019 Accepted: 13 February 2019
Published online: 23 February 2019

© American College of Neuropsychopharmacology 2019

which is believed to reflect the automatic switch in attention caused by the change in the auditory environment due to the deviant stimulus [15, 16]. MMN is thought to have a mediating effect on cognition [17] and is linked with functional outcome in schizophrenia [18]. Another measure of attention that is usually simultaneously assessed with MMN is the P3a amplitude. The P3a amplitude is a positive deflection in the EEG signal after detection of a deviance in an incoming stream of information, and it is thought to represent an orienting reflex [14]. MMN and P3a amplitude deficits are frequently found in schizophrenia patients (for a meta-analysis see Erickson et al. [19]). In two previous studies from our lab we showed that clonidine is able to improve sensori(motor) gating in a group of chronic schizophrenia patients [20, 21]. Currently we report on whether clonidine is also able to normalize MMN and P3a amplitude in the same population of subjects. This is important, since even a small increase in MMN translates to a large positive effect in cognition [22]. Therefore, we studied the effects of 4 different doses of clonidine (25, 50, 75 and 150 µg) on MMN in schizophrenia patients on stable medication. Their results were compared to that of age- and gender-matched healthy controls. Based on the reasoning above we expected to find reduced MMN and P3a amplitude in schizophrenia patients compared to healthy controls, which would be normalized by clonidine.

METHODS

Participants

The study was approved by the Ethics Committee of the Capital Region (H-KF-2006-6813), Copenhagen, according to the ethical principles and guidelines for medical research involving human subjects as stated in the declaration of Helsinki (amendment of Washington, 2002).

Written and oral information was given, after which written informed consent was obtained from all subjects. Twenty chronic, yet clinically stable, medicated male schizophrenia patients between the age of 25 and 50 years were recruited from psychiatric hospitals and outpatient clinics in the Capital Region of Copenhagen. All patients completed the Schedule of Clinical Assessment (SCAN [23]) version 2.1 to confirm their schizophrenia diagnosis, according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria. Exclusion criteria were a history of mental retardation, organic brain damage or organic psychosis and patients who were involuntarily hospitalized. Substance dependence (as defined by DSM-IV) was an exclusion criterion.

The patients were matched to 20 healthy controls (HC) based on age and gender. The healthy controls were recruited from the community and had no current or history of psychiatric illness (confirmed with the SCAN interview). Further exclusion criteria were controls with a history of mental illness in first-degree relatives. All patients and healthy controls passed a physical examination to ascertain a good physical health.

All patients were taking antipsychotic medication during the entire period they participated in the study and, importantly, none of the patients changed medication during that time: 2 patients were treated with typical antipsychotics, 14 with atypical and 3 with a combination of both. Simultaneous treatment with benzodiazepines and antidepressants was allowed: 2 patients were additionally treated with benzodiazepines, 1 patient with antidepressants and 3 patients with a combination of both (only treatment with selective serotonin reuptake inhibitors with low noradrenergic affinity (Ki < 1000 nM) were allowed).

Due to various reasons, not all patients participated in each condition: 1 patient did not participate in the placebo condition, 2 not in the 25 µg condition, 2 not in the 150 µg condition and 1 not in the placebo and 150 µg condition. One patient only participated in the 25 µg condition and was therefore excluded from the analyses. Table 1 shows the characteristics of all subjects.

Experimental design

Patients were tested in a pseudo-randomized, double-blind, placebo-controlled design on 5 different occasions (with a minimum of 1 week between test days) with the MMN paradigm from the Copenhagen Psychophysiological Test Battery (CPTB). At 4 h prior to testing, patients were administered an opaque white capsule containing either a placebo (non psycho-active substance) or a single dose of 25, 50, 75 or 150 µg (order was randomized in

Table 1. Demographic and neurophysiological characteristics of the healthy controls and the patients

	Controls ($n = 20$)	Patients ($n = 19$)				
		Placebo ($n = 17$)	25 µg ($n = 17$)	50 µg ($n = 19$)	75 µg ($n = 19$)	150 µg ($n = 15$)
Mean age (SD)	33.45 (6.41)	37.78 (6.21)*				
Antipsychotic medication, typical/atyical/both		2/14/3				
Mean PANSS scores (SD)						
Positive		12.82 (5.26)	14.47 (7.09)	12.67 (4.52)	13.78 (6.70)	11.50 (2.28)
Negative		13.82 (5.08)	16.06 (4.42)	15.39 (5.95)	15.38 (5.09)	14.13 (4.76)
General		24.24 (6.58)	25.82 (7.00)	25.11 (7.18)	25.67 (6.96)	23.44 (4.44)
Total		50.76 (14.58)	56.88 (15.70)	53.11 (14.57)	54.83 (16.48)	48.94 (9.07)
Mean MMN amplitudes (SD)						
Freq deviant	−2.32 (0.82)	−2.25 (1.00)	−2.86 (1.27)	−2.65 (1.35)	−2.77 (1.55)	−3.16 (1.17)
Duration deviant	−4.03 (1.29)	−2.82 (1.33)*	−2.67 (1.64)*	−3.01 (1.62)*	−2.68 (1.27)*	−3.22 (1.64)
FreqDur deviant	−3.61 (1.04)	−2.84 (1.08)*	−3.46 (1.93)	−3.22 (1.56)	−3.06 (1.27)	−3.36 (1.24)
Mean P3a amplitudes (SD)						
Freq deviant	2.81 (1.31)	2.68 (1.02)	2.36 (1.16)	2.57 (0.97)	2.40 (1.11)	2.90 (1.27)
Duration deviant	3.58 (1.55)	2.56 (1.22)*	1.97 (1.15)*	2.84 (1.33)	2.40 (1.07)*	2.76 (1.52)
FreqDur deviant	4.61 (1.40)	3.16 (1.44)**	2.70 (1.23)**	3.40 (1.32)**	2.99 (1.14)**	3.16 (1.44)**

PANSS Positive and Negative Symptom Scale, *MMN* mismatch negativity, *Freq* frequency, *FreqDur* frequency–duration
*Significant group difference at $p < 0.05$
**Significant group difference at $p < 0.001$

such a way that each patient received each dose once) clonidine (Catapresan®) on top of their usual medication on each occasion. Before each occasion the patients' symptomatology was assessed with the Positive and Negative Symptom Scale (PANSS [24]).

MMN paradigm

The paradigm has been described before [25]. In short, auditory stimuli were presented binaurally by a computer running Presentation® software (Neurobehavioral Systems Inc., Albany, CA, USA.). The paradigm consisted of 1800 stimuli with 4 types of stimuli, i.e., 1 standard and 3 types of deviants. Standard stimuli were 1000 Hz pure tones with an intensity of 50 dB and duration of 50 ms and occurred with a probability of 82%. Within this sequence of standard stimuli, three types of deviants were presented each with a probability of 6% and an intensity of 75 dB: 1200 Hz frequency deviants with a duration of 50 ms, 1000 Hz duration deviants with a duration of 100 ms and 1200 Hz frequency–duration deviants with a duration of 100 ms. The interstimulus interval was randomized between 400 and 500 ms. Subjects were requested to ignore all stimuli and therefore watched a muted nature documentary. Total duration of the MMN task was approximately 15 min.

Signal recording and processing

EEG was recorded with BioSemi® hardware (Amsterdam, The Netherlands) using a cap with 64 active-two electrodes. To minimize effects of multiple testing, only data from the electrodes relevant for the present study were analyzed (i.e., where MMN amplitude reached maximum amplitude): midline electrode FCz.

BESA software (version 6.0, MEGIS Software GmbH, Gräfelfing, Germany) was used for further processing and eventual scoring of the EEG signals. First, data were resampled from the original 2 kHz to 250 Hz to allow easier file handling. Second, data were corrected for eye artifacts using the adaptive method of BESA. Third, the data were epoched (from 100 ms prestimulus to 900 ms poststimulus) and corrected for movement (or other paradigm unrelated) artifacts, by removing those epochs from the database that contained amplitude differences of 75 µV between maximum and minimum for the MMN relevant time window (see below). Subsequently, data were band-pass filtered (high-pass: 0.5 Hz, low-pass: 40 Hz), after which MMN of each of the three deviant types was expressed as the average event-related potential (ERP) to the relevant deviant stimuli, subtracted with the average ERP to standard stimuli for each subject separately. Linked mastoids were used for reference purposes. Last, MMN amplitudes were scored as the minimum amplitude within a window between 75 and 300 ms, while P3a was scored as the maximum amplitude within a time window between 175 and 375 ms.

Statistical analyses

All statistical analyses were conducted using R (version 3.4.1). Differences in age between the patient group and the healthy controls were examined with an independent sample *t*-test. The Shapiro–Wilk test was used to assess normality of the data and appropriate tests were used accordingly. The patients were slightly yet significantly older than the HC ($t(37) = 2.15$, $p = 0.04$) and therefore age was initially included as a covariate; however, given that this covariate never reached statistical significance, we excluded it from the analyses.

Group differences between healthy controls and the patients' placebo condition on MMN and P3a amplitude data were analyzed using multivariate analysis of variance (MANOVA), with the independent variable "Group" (patients vs. healthy controls) and the dependent variables "deviant-type" (frequency, duration or frequency–duration deviant).

We analyzed the effects of clonidine on MMN and P3a amplitude for "deviant-type" with linear mixed-effects (LME) models (*lme4* in R [26]), with frequency, duration and frequency–duration deviants as dependent variables in three different models. The repeated measures factor in each model was "Dose" (placebo, 25, 50, 75 or 150 µg clonidine) and random effect factor was "Subject". *The p* values were obtained from likelihood ratio tests of the full model which included the effect "Dose" against the null model without the effect of "Dose". Only when a main effect was found, post-hoc pairwise analyses (*p* values Tukey-adjusted) were performed.

To compare the effects of clonidine with respect to the healthy control data, we performed independent sample *t*-tests only with those doses that had a normalizing effect on basic sensory processing of patients in our previous research (25, 50 or 75 µg clonidine [20, 21]).

RESULTS

Demographics

The patients' medical treatment did not change during their participation in this study and, more importantly, their clinical symptoms remained stable throughout this period (see Table 1, also for more demographics). At the end of each test day, patients were asked if they thought to have received either placebo or clonidine. In addition, after completion of all test days, patients were asked if they could indicate which of the test days they had received either placebo or the highest dose of clonidine; none of their guesses surpassed chance levels of significance.

Electrophysiology

MMN. The MANOVA revealed a significant group difference between the healthy controls and patients in the placebo condition ($F(3, 33) = 3.95$, $p = 0.016$). Further analyses of this result with separate univariate ANOVAs indicated significant group differences on MMN induced by Duration (DurMMN) ($F(1, 35) = 7.73$, $p = 0.008$, $d = 0.92$) and Frequency–Duration (FreqDurMMN) deviants ($F(1, 35) = 4.86$, $p = 0.034$, $d = 0.73$), but not by the Frequency deviant (FreqMMN) ($F(1, 35) = 0.05$, $p = 0.821$, $d = 0.08$), indicating less MMN in the patient group in spite of their current medical treatment (see also Table 1 and Fig. 1). No significant group differences in MMN latency differences on baseline measures were found for any of the types of deviants ($p > 0.517$, $d < 0.36$). These results did not change much when we analyzed *mean* MMN amplitude instead of the above described *maximum* MMN amplitude (time windows: FreqDev = 50–200 ms; DurDev = 100–230 ms; FreqDurDev = 70–220 ms), except that the group difference in DurMMN and FreqDurMMN only reached trend level of significance in the comparison between the patients' placebo condition and the healthy controls ($t < 1.92$, $p = 0.06$).

Although on average clonidine increased MMN in our patients, this did not reach statistical significance for any of the 4 different dosages or 3 types of deviants compared to placebo (DurMMN: $\chi^2(4) = 2.49$, $p = 0.65$; FreqMMN: $\chi^2(4) = 6.32$, $p = 0.18$; FreqDurMMN: $\chi^2(4) = 4.80$, $p = 0.31$). For Grand Average waves and supplementary statistics of the LMM of the different doses of clonidine, see Supplementary Figure S1 and Table S1.

The above described planned comparisons between healthy controls and the 3 different doses of clonidine in patients showed that the group differences in DurMMN remained significant ($p < 0.04$, $d > 0.7$), but disappeared for FreqDurMMN for all three (25, 50 and 75 µg) analyzed dosages ($t < 1.49$, $p > 0.15$, $d < 0.72$).

P3a. Similar as for MMN, the MANOVA on P3a data indicated a significant group difference between the healthy controls and the patients in the placebo condition ($F(3, 33) = 4.592$, $p = 0.009$). Subsequent univariate ANOVAs indicated smaller P3a amplitude for the patient group on the Duration (DurP3a) and the Frequency–Duration (FreqDurP3a) deviants (($F(1, 35) = 4.828$, $p = 0.035$, $d = 0.73$) and ($F(1, 35) = 9.549$, $p = 0.004$, $d = 1.02$)

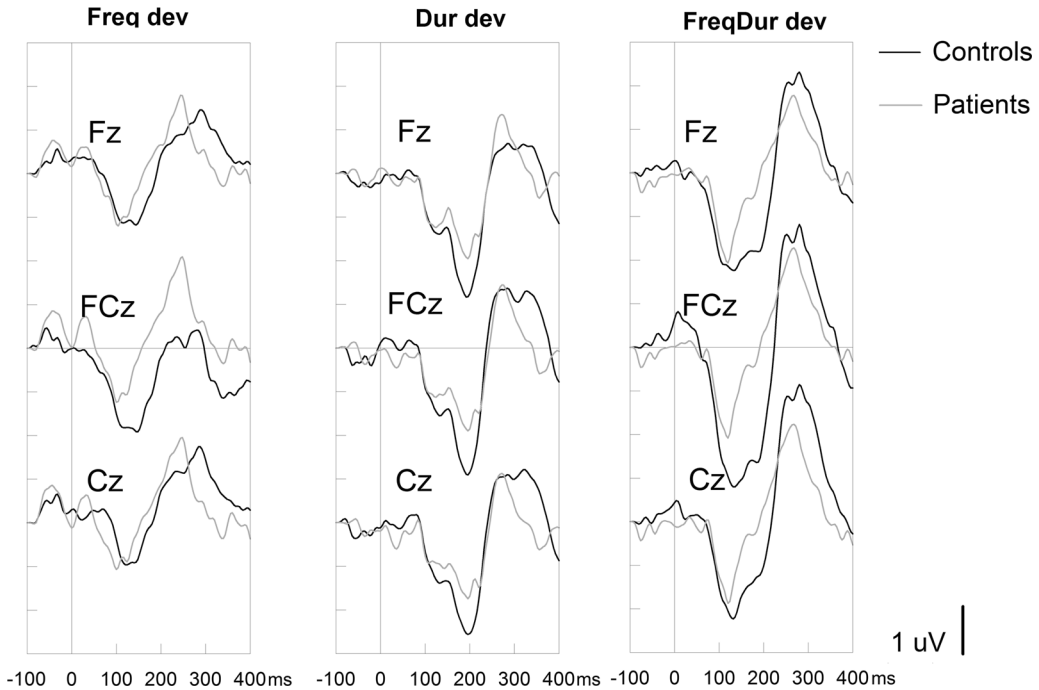

Fig. 1 Grand average waves for the healthy controls and the placebo condition of the patients of mismatch negativity (MMN) and P3a amplitude elicited by the three different deviant types on three electrodes (Fz, FCz, Cz). The *x*-axis depicts time in milliseconds. This figure indicates peak MMN at electrode FCz

respectively), while no significant differences were found for the Frequency (FreqP3a) deviant ($F(1, 35) = 0.096$, $p = 0.759$, $d = 0.11$) (see also Table 1). No significant group differences in P3a latency were found at baseline, for any of the 3 deviants ($p > 0.159$, $d < 0.47$).

No significant effect of dose on P3a amplitude was found for any of the deviant types in patients (DurP3a: $\chi^2(4) = 8.265$, $p = 0.08$; FreqP3a: $\chi^2(4) = 2.169$, $p = 0.70$; FreqDurP3a: $\chi^2(4) = 4.700$, $p = 0.32$).

For P3a amplitude, most of the significant group differences found at baseline persisted at follow-up ($t > 2.776$, $p < 0.009$, $d < 0.88$) except for DurP3a in the 50 µg condition where it disappeared ($t(37) = 1.597$, $p = 0.119$, $d = 0.51$). See also Table 1.

DISCUSSION

In the current study we investigated the effects of clonidine on MMN and P3a amplitude in patients with schizophrenia on stable medication. Despite their medication, patients showed significantly reduced levels of MMN and P3a amplitude, although only to duration and combined frequency–duration deviants and not to frequency deviants only. This is in line with other studies showing that DurMMN is usually more pronounced in schizophrenia than FreqMMN [27, 28] (for a review see Erickson et al. [19]). On average, clonidine in comparison to placebo increased MMN of the patients, yet this did not reach statistical significance. Nevertheless, this increase in MMN was to such an extent that it was no longer significantly different from the healthy controls anymore, yet only for the combined (FreqDur) deviant. Only the 50 and 150 µg dosages of clonidine increased DurP3a amplitude in patients to a level that was non-significantly different from healthy controls.

Literature on the noradrenergic involvement in MMN is sparse; in fact, to our knowledge only one study reported on the implication of noradrenaline in the generation of MMN and they did not find evidence for this in healthy subjects [29]. Similarly, evidence of noradrenergic involvement in the generation of P3a amplitude is scarce; only one study reported on the effects of clonidine on P3a amplitudes in healthy volunteers [30], where they found that clonidine reduced P3a amplitude, while yohimbine, an α2 antagonist, increased P3a amplitude relative to a placebo. It must be noted that the above described studies (MMN and P3a amplitude) used a relative high dose of clonidine (0.15 mg and 0.2 mg respectively), which, in a healthy population with a presumably balanced noradrenergic system, would normally induce substantial levels of sedation. The resulting low levels of noradrenaline in the PFC might therefore have caused unresponsiveness to the incoming stimuli and hence resulted in the given outcomes [7, 30]. In contrast, our current study shows that noradrenergic modulation with clonidine in a population with a presumed NA imbalance in their central nervous system results in normalization of MMN amplitude (and to a lesser extend increased P3a amplitude).

Whereas the involvement of noradrenaline in MMN is currently not well studied yet, there is abundant evidence for involvement of *N*-methyl-D-aspartate (NMDA) in the generation of MMN [31–34]. Given that clonidine increased certain types of MMN and P3a to such levels in our current study that it was indistinguishable from healthy controls, it indicates that there is at least some influence of NA on MMN. Together with evidence that dopamine [35], serotonin [36, 37] and nicotine [38, 39] also appear to be involved in MMN generation, this suggests that glutamatergic transmission is likely not the only factor of importance in the generation of MMN, although it cannot be ruled out that these other neurotransmitters influence MMN through mediation of glutamatergic activity. Interestingly however, there is, besides a temporal, also a frontal generator of MMN which is associated with the attentive component of the MMN [15, 16, 40]. As mentioned above, it is assumed that clonidine interacts with the balance between α1 and α2 activity in the PFC [6], while all the aforementioned neurotransmitter systems also have a strong impact on PFC functions; alternatively therefore, they may exert their impact on MMN through this frontal MMN generator.

To date, we do not fully understand the neural bases of sensory and cognitive processing, and therefore we can only speculate about the clinical implications of our current and previously [20, 21] found normalizing effects of clonidine on disturbed basic sensory information processing in schizophrenia. However, given that several different single dosages of clonidine added to the medical treatment of our chronic patients with schizophrenia so far have only shown beneficial effects on the parameters that we studied, it is worth the effort of studying prolonged periods of add-on medication with clonidine. After all, these basic information processes are associated with higher up phenomena such as cognition [41–43], or even daily life functions [17], and they were still disturbed in our clinically stable medicated patients before we added clonidine to their treatment. It is further noteworthy that none of our patients could distinguish whether they received additional placebo or clonidine (not even in the 0.15 mg condition), and thus, in other words, it was well taken.

There are some strengths and limitations to this study. Although our study consisted of a relatively small sample size (patients $N = 19$, HC $N = 20$), the within-subjects design where the patients randomly received not only one but four different doses of clonidine can be considered a strength. A limitation might have been that controls only underwent one experimental assessment. However, MMN has a high test retest reliability in both healthy volunteers and schizophrenia patients on stable medication [44]. This, and the fact that the order in which our patients received the different doses of clonidine or placebo was random yet balanced, makes it unlikely that test effects have played an important role in our current or previous results. Another limitation is the inclusion of only male schizophrenia patients into the study. Therefore, the current findings might or might not be applicable to female patients with schizophrenia.

The current study showed that at least certain types of MMN can be normalized in patients with schizophrenia on stable medication after adding single, low doses of clonidine to their current medication. Given that low dosages of clonidine are well taken without noticeable side effects, together with our previous findings indicating that also sensori(motor) gating deficits of these same patients were normalized by clonidine, this warrants research on longer-term treatment augmentation with clonidine of schizophrenia patients.

FUNDING AND DISCLOSURE

The study was sponsored by The Danish Council for Independent Research (Medical Sciences, grant number: 271-06-0308) and the Lundbeck foundation (grant number: R25-A2701). Dr. Glenthøj is the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. Her group has also received a research grant from Lundbeck A/S for another independent investigator initiated study. All grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them. The authors declare no competing interests.

ACKNOWLEDGEMENTS

The authors would like to thank the contributions of Gitte Saltoft Andersen and Katherina Alfsen.

ADDITIONAL INFORMATION

Supplementary Information accompanies this paper at (https://doi.org/10.1038/s41386-019-0351-6).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Kahn RS, Keefe RSE. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry. 2013;70:1107–12. https://doi.org/10.1001/jamapsychiatry.2013.155
2. Light GA, Swerdlow NR, Thomas ML, Calkins ME, Green MF, Greenwood TA, et al. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. Schizophr Res. 2015;163:63–72. https://doi.org/10.1016/j.schres.2014.09.042
3. Strassnig MT, Raykov T, O'Gorman C, Bowie CR, Sabbag S, Durand D, et al. Determinants of different aspects of everyday outcome in schizophrenia: the roles of negative symptoms, cognition, and functional capacity. Schizophr Res. 2015;165:76–82. https://doi.org/10.1016/j.schres.2015.03.033
4. Borodovitsyna O, Flamini M, Chandler D. Noradrenergic modulation of cognition in health and disease. Neural Plast.2017;2017:6031478
5. Arnsten AFT. Adrenergic targets for the treatment of cognitive deficits in schizophrenia. Psychopharmacology (Berl).2004;174:25–31.
6. Arnsten AFT. Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": a rational bridge between genetics and the symptoms of mental illness. Cereb Cortex. 2007;17 Suppl 1: i6–i15. https://doi.org/10.1093/cercor/bhm033
7. Arnsten AFT. Prefrontal cortical network connections: key site of vulnerability in stress and schizophrenia. Int J Dev Neurosci. 2011;29:215–23. https://doi.org/10.1016/j.ijdevneu.2011.02.006
8. Berridge CW, Spencer RC. Differential cognitive actions of norepinephrine a2 and a1 receptor signaling in the prefrontal cortex. Brain Res. 2016;1641:189–96. https://doi.org/10.1016/j.brainres.2015.11.024
9. Fields RB, Van Kammen DP, Peters JL, Rosen J, Van Kammen WB, Nugent A, et al. Clonidine improves memory function in schizophrenia independently from change in psychosis. Prelim Find Schizophr Res. 1988;1:417–23. https://doi.org/10.1016/0920-9964(88)90024-2
10. Friedman JI, Adler DN, Davis KL. The role of norepinephrine in the pathophysiology of cognitive disorders: potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. Biol Psychiatry. 1999;46:1243–52. https://doi.org/10.1016/S0006-3223(99)00232-2
11. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neurosci Biobehav Rev. 2011;35:573–88. https://doi.org/10.1016/j.neubiorev.2010.07.001.
12. Insel TR. Rethinking schizophrenia. Nature. 2010;468:187–93. https://doi.org/10.1038/nature09552
13. Ramos BP, Arnsten AFT. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacol Ther. 2007;113:523–36. https://doi.org/10.1016/j.pharmthera.2006.11.006
14. Näätänen R, Paavilainen P, Rinne T, Alho K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin Neurophysiol. 2007;118:2544–90. https://doi.org/10.1016/j.clinph.2007.04.026
15. Giard MH, Perrin F, Pernier J, Bouchet P. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology. 1990;27:627–40. https://doi.org/10.1111/j.1469-8986.1990.tb03184.x
16. Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNM) elicited by sound changes. Ear Hear. 1995;16:38–51. https://doi.org/10.1097/00003446-199502000-00004
17. Thomas ML, Green MF, Hellemann G, Sugar, CA, Tarasenko M, Calkins ME, et al. Modeling deficits from early auditory information processing to psychosocial functioning in schizophrenia. JAMA Psychiatry. 2017;74:37–46. https://doi.org/10.1001/jamapsychiatry.2016.2980
18. Hamilton HK, Perez VB, Ford JM, Roach BJ, Jaeger J, Mathalon DH. Mismatch negativity but not P300 is associated with functional disability in schizophrenia. Schizophr Bull. 2018;44:492–504. https://doi.org/10.1093/schbul/sbx104
19. Erickson MA, Ruffle A, Gold JM. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. Biol Psychiatry. 2016;79:980–7. https://doi.org/10.1016/j.biopsych.2015.08.025
20. Oranje B, Glenthøj BY. Clonidine normalizes sensorimotor gating deficits in patients with schizophrenia on stable medication. Schizophr Bull. 2013;39:684–91. https://doi.org/10.1093/schbul/sbs071
21. Oranje B, Glenthøj BY. Clonidine normalizes levels of P50 gating in patients with schizophrenia on stable medication. Schizophr Bull. 2014. https://doi.org/10.1093/schbul/sbt144
22. Swerdlow NR, Bhakta SG, Light GA. Room to move: plasticity in early auditory information processing and auditory learning in schizophrenia revealed by acute

pharmacological challenge. Schizophr Res. 2018. https://doi.org/10.1016/j.schres.2018.03.037
23. Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, et al. Scan: Schedules for clinical assessment in neuropsychiatry. Arch Gen Psychiatry. 1990;47:589–93. https://doi.org/10.1001/archpsyc.1990.01810180089012
24. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res. 1988;23:99–110. https://doi.org/10.1016/0165-1781(88)90038-8
25. Rydkjær J, Møllegaard Jepsen JR, Pagsberg AK, Fagerlund B, Glenthøj BY, Oranje B. Mismatch negativity and P3a amplitude in young adolescents with first-episode psychosis: a comparison with ADHD. Psychol Med. 2017;47:377–88. https://doi.org/10.1017/S0033291716002518
26. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67. https://doi.org/10.18637/jss.v067.i01.
27. Todd J, Michie PT, Schall U, Karayanidis F, Yabe H, Näätänen R. Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. Biol Psychiatry. 2008;63:58–64. https://doi.org/10.1016/j.biopsych.2007.02.016
28. Todd J, Michie PT, Schall U, Ward PB, Catts SV. Mismatch negativity (MMN) reduction in schizophrenia—impaired prediction-error generation, estimation or salience? Int J Psychophysiol. 2012;83:222–31. https://doi.org/10.1016/j.ijpsycho.2011.10.003
29. Hansenne M, Pinto E, Scantamburlo G, Couvreur A, Reggers J, Fuchs S, et al. Mismatch negativity is not correlated with neuroendocrine indicators of catecholaminergic activity in healthy subjects. Hum Psychopharmacol. 2003;18:201–5. https://doi.org/10.1002/hup.468
30. Turetsky BI, Fein G. α2-noradrenergic effects on ERP and behavioral indices of auditory information processing. Psychophysiology. 2002;39:147–57. https://doi.org/10.1017/S0048577202991298
31. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers. Arch Gen Psychiatry. 2000;57:1139–47. https://doi.org/10.1001/archpsyc.57.12.1139
32. Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. Biol Psychiatry. 2002;51:400–6. https://doi.org/10.1016/S0006-3223(01)01242-2
33. Kantrowitz JT. N-methyl-d-aspartate-type glutamate receptor modulators and related medications for the enhancement of auditory system plasticity in schizophrenia. Schizophr Res. 2018. https://doi.org/10.1016/j.schres.2018.02.003
34. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc Natl Acad Sci USA. 1996;93:11962–7. https://doi.org/10.1073/pnas.93.21.11962
35. Kähkönen S, Ahveninen J, Pekkonen E, Kaakola S, Huttunen J, Ilmoniemi RJ, et al. Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study. Clin Neurophysiol. 2002;113:1894–902. https://doi.org/10.1016/S1388-2457(02)00305-X
36. Wienberg M, Glenthoj BY, Jensen KS, Oranje B. A single high dose of escitalopram increases mismatch negativity without affecting processing negativity or P300 amplitude in healthy volunteers. J Psychopharmacol. 2010;24:1183–92. https://doi.org/10.1177/0269881109102606
37. Oranje B, Jensen K, Wienberg M, Glenthøj BY. Divergent effects of increased serotonergic activity on psychophysiological parameters of human attention. Int J Neuropsychopharmacol. 2008;11:453–63. https://doi.org/10.1017/S1461145707008176
38. Baldeweg T, Wong D, Stephan KE. Nicotinic modulation of human auditory sensory memory: evidence from mismatch negativity potentials. Int J Psychophysiol. 2006;59:49–58. https://doi.org/10.1016/j.ijpsycho.2005.07.014
39. Dulude L, Labelle A, Knott VJ. Acute nicotine alteration of sensory memory impairment in smokers with schizophrenia. J Clin Psychopharmacol. 2010;30:541–8. https://doi.org/10.1097/JCP.0b013e3181f0c9c6
40. Halgren E, Marinkovic K, Chauvel P. Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroencephalogr Clin Neurophysiol. 1998;106:156–64. https://doi.org/10.1016/S0013-4694(97)00119-3
41. Sánchez-Morla EM, Santos JL, Aparicio A, García-Jiménez MÁ, Soria C, Arango C. Neuropsychological correlates of P50 sensory gating in patients with schizophrenia. Schizophr Res. 2013;143:102–6. https://doi.org/10.1016/j.schres.2012.10.017
42. Bak N, Ebdrup BH, Oranje B, Fagerlund B, Jensen MH, Düring SW, et al. Two subgroups of antipsychotic-naive, first-episode schizophrenia patients identified with a Gaussian mixture model on cognition and electrophysiology. Transl Psychiatry. 2017;7:e1087–8. https://doi.org/10.1038/tp.2017.59
43. Braff DL, Geyer MA. Sensorimotor gating deficits and schizophrenia: human and animal studies. Arch Gen Psychiatry. 1990;2:181–8.
44. Light GA, Swerdlow NR, Rissling AJ, Radant A, Sugar CA, Sprock J, et al. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. PLoS One 2012;7:e39434. https://doi.org/10.1371/journal.pone.0039434.