The effects of imipramine on P50 suppression, prepulse inhibition and habituation of the startle response in humans

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Abstract
Schizophrenic patients exhibit impairments in filtering of sensory information, as can be assessed by use of prepulse inhibition (PPI) of the acoustic startle response and P50 suppression paradigms. In the treatment of negative symptoms or depressive syndromes during the course of schizophrenia antidepressants are often combined with antipsychotic medication. However, antidepressants increase monoaminergic activity, which has been suggested to decrease sensory gating, although these presumptions are mostly based on results from animal studies. Currently, little is known about monoaminergic modulation of sensory filtering in humans, and the few reports that can be found in literature show discrepancies with animal studies. The current study was designed to study the effects of increased monoaminergic activity on sensory filtering and habituation of healthy volunteers. In a double-blind, placebo-controlled crossover design, 20 healthy male volunteers received either placebo or a dose of 50 mg imipramine (a dual-acting antidepressant), after which they were tested in a P50 suppression paradigm, a PPI paradigm, and an habituation of the startle reflex paradigm. Imipramine significantly decreased PPI as well as P50 suppression. No significant differences between the two treatments were observed on habituation of the acoustic startle reflex. Since sensory filtering is usually already reduced in patients with schizophrenia, the current results call for caution in the widespread use of dual-acting antidepressants in the treatment of depressed or negative symptoms in these patients.

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Introduction
Disturbances in attention and information processing are proposed to be fundamental causes of symptoms in schizophrenia (Braff and Geyer, 1990). Clinical reports have long described how schizophrenic patients are unable to direct their attention focally. It seems that they pay attention to every stimulus and therefore are unable to concentrate (Bleuler, 1937; Kraepelin, 1913; McGhie and Chapman, 1961). This incapacity to filter out irrelevant stimuli is hypothesized to cause an overload of sensory information, which may underlie the positive symptoms as seen in schizophrenia (Braff and Geyer, 1990; Freedman et al., 1991). In addition, it is likely that the disorganized symptoms of schizophrenia (e.g. thought disorder) are most directly related to gating deficits (see Perry et al., 1999).

Prepulse inhibition (PPI) of the startle reflex and P50 suppression paradigms have been proposed to quantify the ability to filter sensory information. The PPI paradigm is based on the startle response, i.e. the response seen when a sudden and intense stimulus is given. In human studies, the startle reflex is usually measured as the electromyographic (EMG) response of m. orbicularis oculi. If the startle-eliciting stimulus is preceded (30–500 ms) by a weak stimulus (prepulse) the startle response is reduced (Graham, 1975). This is known as PPI and is thought to be an operational measure of sensorimotor gating. In P50 suppression, two identical auditory stimuli are presented close together (often 500 ms apart). The electroencephalographic (EEG) response seen ~50 ms after each
stimulus is the P50 response. P50 suppression (sensory gating) is the phenomenon when the P50 amplitude to the first, or conditioning, stimulus is larger than to the second, or testing, stimulus (for a review see Light and Braff, 1999). Habituation (the startle response decreases when a series of repeated startle-eliciting stimuli are presented) is another example of the plasticity of the startle response and is also believed to be a way of protecting the higher cortical areas of the brain from irrelevant stimuli (Geyer and Braff, 1982).

Schizophrenic patients show reduced PPI and P50 suppression compared to healthy controls [PPI: Braff et al., 1992, 2001 (review); Geyer and Braff, 1982; P50 suppression: Adler et al., 1982; Nagamoto et al., 1989, 1991]. Studies investigating habituation in schizophrenic patients have shown contradictory results, some demonstrating habituation deficits (Bolino et al., 1992; Geyer and Braff, 1982) while others not (Braff et al., 1999; Cadenhead et al., 2000). Numerous animal studies have been performed in order to investigate the neuro-anatomical and physiological basis of PPI and P50 suppression [PPI: Geyer et al., 2001 (review); P50 suppression: Adler et al., 1998 (review)]. Several neurotransmitters, such as dopamine, acetylcholine, GABA, noradrenaline, serotonin and glutamate have been shown to alter PPI in rodents (for a review see Geyer et al., 2001). Discrepancies between animal and human studies on sensorimotor gating have also been found, e.g. serotonin decreases PPI in rodents (Dulawa et al., 1997, 1998; Rigdon and Weatherspoon, 1992), but seems to increase or to have no effect on PPI in humans (Graham et al., 2002; Liechti et al., 2001). This demonstrates that human studies are necessary if the neural basis of sensorimotor gating, and information processing deficits in schizophrenia, is to be determined.

In schizophrenia, abnormalities of dopaminergic, serotonergic and noradrenergic neurotransmission have been proposed to be the core disturbances leading to the disease (Heinz et al., 2003; Yamamoto et al., 1994). To treat negative symptoms or depressive syndromes in schizophrenia antidepressants are often combined with antipsychoptic medication. Antidepressants have their primary action on the metabolism, reuptake or selective receptor antagonism of serotonin, noradrenaline or both. Since sensory filtering is already disturbed in schizophrenia, it is important to know what effects these antidepressants have on the filtering of sensory information. Only a few human studies have examined the effect of antidepressants and other compounds targeting the serotonergic or noradrenergic systems, on sensori(motor) gating. Currently, the effects of serotonin on gating functions are inconclusive: some studies report serotonin to improve gating (Gouzoulis-Mayfrank et al., 1998; Liechti et al., 2001; Liechti and Vollenweider, 2001), while others report no effect of serotonin on gating functions (Phillips et al., 2000; Quednow et al., 2004). Interestingly, serotonin antagonists seem to have the same inconsistent effect on PPI (Adler et al., 2005; Graham et al., 2002; Liechti and Vollenweider, 2001). In a study of Riba et al. (2002), P50 suppression was diminished by the psychotropic plant ayahuasca which, among others contains N,N-dimethyltryptamine, a 5-HT2A/2C receptor agonist. In contrast to the serotonergic system, the effects of noradrenaline on sensori(motor) gating seems to be more consistent: increased noradrenergic activity seems to disrupt both PPI (Oranje et al., 2004; Quednow et al., 2004) and P50 suppression (Adler et al., 1994). Habituation seems unaffected by noradrenergic activity (Oranje et al., 2004), but seems sensitive to the level of serotonin (Quednow et al., 2004).

In the present study the effect of imipramine on sensori(motor) gating was investigated. Imipramine is a dual-acting, tricyclic antidepressant, which blocks nearly the same amount of central noradrenaline reuptake as central serotonin reuptake. It was hypothesized that imipramine would diminish sensory (P50 suppression) and sensorimotor gating (PPI) by increasing noradrenergic activity, and would diminish habituation by increasing serotonergic activity.

Methodology

Subjects

The study was approved by the Committee for Biomedical Research Ethics, Copenhagen, with regards to the ethical principles 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. Male volunteers aged between 18 and 35 yr, all non-smokers, were recruited via a university newspaper. Only physically healthy males who were not taking any prescription drugs, were not abusing alcohol or drugs and did not have a personal or family history of psychiatric illness in first-degree relatives were included. Physical and mental health history and absence of a history of drug and alcohol abuse were ascertained by use of the Schedule for Clinical Assessment in Neuropsychiatry, version 2.0 (SCAN;
Wing et al., 1990). Blood pressure was measured, and all subjects underwent a routine electrocardiogram (ECG) recording to ensure that the subjects did not show long QT syndrome or hypotension which both could be worsened by imipramine. To screen for hearing deficits, subjects were tested at 500, 1000 and 6000 Hz (40 dB). Twenty subjects fulfilled the inclusion criteria, and were subsequently included in the study. None of these subjects had ever previously participated in other sensory gating, sensorimotor gating and habituation studies. One subject became severely nauseated during test day 1 (the imipramine session), probably due to a vaso-vagal attack and was therefore excluded. The recording of one PPI session of one subject was lost due to hardware failure, subsequently this subject was excluded entirely for PPI analysis. Furthermore, data from two subjects were excluded because they showed prepulse facilitation, instead of prepulse inhibition, to the 85 dB/120 ms prepulse-pulse combination in the placebo session, while under normal circumstances healthy subjects show maximum PPI to this prepulse-pulse combination (Graham, 1975; for reviews see Braff et al., 2001; Dawson et al., 1999). This left 16 datasets for PPI and habituation assessment and 19 datasets for P50 suppression assessment. The remaining subjects had a mean age of 24.5 (s.d. = 2.3) yr for P50 suppression, and 25.6 (s.d. = 2.2) yr for P50 suppression.

**Experimental design**

In a balanced, double-blind, placebo-controlled crossover design healthy male volunteers were tested on two occasions separated by a minimum of 2 wk, in P50 suppression, habituation and PPI paradigms, after oral administration of either placebo tablets (lactate tablets) or 50 mg imipramine. The order of the paradigms was balanced over subjects, but the same for both treatment sessions of each individual subject. Serum imipramine was measured at the end of each test session. To rule out any concealed recent drug use the subjects had their urine screened for opium, cannabis, benzodiazepines and amphetamines at each test session. The test sessions were performed at the research ward at the Department of Psychiatry, Bispebjerg University Hospital, Copenhagen. The subjects were tested at the same time of day on both occasions and were requested to fast for 8 h before the test sessions. To ensure blindedness, both placebo and imipramine tablets were put in identical opaque white gelatin capsules. The psychophysiological assessments started 1 h after intake of the capsules, which coincided with the expected maximum plasma level of imipramine (T_{max}) (Ullmann et al., 2001).

**Paradigms**

All auditory stimuli were presented by a computer running Presentation® software (soundcard Creative Soundblaster®, 5.1; Neurobehavioral Systems Inc., Albany, CA, USA) and presented binaurally through stereo insert earphones (Eartone ABR; C and H Distributors Inc., Milwaukee, WI, USA). The software and hardware settings were calibrated by means of an artificial ear (Brüel and Kjær, type 2133; Brüel and Kjær, Naerum, Denmark) in order to make sure that the stimulus intensities at the subject’s ears were the intended intensities.

**PPI and habituation**

Subjects were seated in a comfortable armchair in a room with a sound level below 40 dB and situated adjacent to the control room. Subjects were instructed to sit still, to keep their eyes fixed on a spot on the wall directly in front of them and to stay awake. Prepulse inhibition and habituation testing was initiated with 5 min of acclimatization to a background noise (70 dB white noise) after which three experimental blocks of stimuli were super-imposed on the background noise. Blocks 1 and 3 were used to assess habituation of the acoustic startle reflex (ASR). They were identical and consisted of eight pulse-alone trials (white noise with an intensity of 115 dB, a duration of 20 ms, and with instant rise and fall) with randomized inter-trial intervals between 10 s and 20 s, to assess habituation. Block 2 consisted of 50 trials presented in a pseudo-randomized order (pulse-alone trials were never in direct succession of each other), to assess PPI of the ASR. Prepulses consisted of bursts of white noise with intensities of either 6 dB or 15 dB above background with a duration of 20 ms. Stimulus onset asynchrony (SOA) in prepulse-pulse trials was either 60 ms or 120 ms, while inter-trial intervals were randomized between 10 s and 20 s. Randomized across the session, 10 pulse-alone and 10 of each prepulse-pulse combination, based on SOA and intensity (60 ms/76 dB, 60 ms/85 dB, 120 ms/76 dB, 120 ms/85 dB), were presented. PPI and habituation assessment took ~25 min.

**P50 suppression**

The test session consisted of three identical blocks of 40 click-pairs; the subject was requested to count the number of click-pairs. Following each block the subject was asked how many pair of clicks he had
counted in the preceding block (this was done to avoid drowsiness). Each click had a duration of 1.5 ms and a sound intensity of 80 dB. The inter-stimulus interval (ISI) was 500 ms and all click-pairs were separated by 10 s.

**Signal recording**

EEG recordings were performed with BioSemi® hardware (BioSemi, Amsterdam, The Netherlands) using a cap with 64 Active Two electrodes (Metting van Rijn et al., 1996), arranged according to the 10–20 system. However, only data from the electrode relevant for the present study were analysed, i.e. the midline electrode Cz, where the maximum amplitude for the P50 ERP was expected (Clementz et al., 1998). A total of eight facial electrodes were attached for EMG recordings and reference purposes. Three reference electrodes were attached: two on the mastoids (one on the left and one on the right) and one on the tip of the nose. Of the remaining five electrodes, two electrodes were placed under the right eye, one aligned with the pupil, the other electrode positioned just laterally (for PPI and habituation assessment), two were placed at the outer canthus of each eye [for horizontal electro-oculogram (HEOG) assessment], and one supra orbital [for vertical electro-oculogram (VEOG) assessment]. Sampling began immediately before an experimental block started and lasted until the block ended. Auditory stimuli were presented binaurally through insert headphones. All signals were digitized online at a rate of 4096 Hz, and a low-pass setting of 1/5 of the AD rate.

**Signal analysis**

Analysis of PPI and habituation started by filtering the data offline between 25 Hz and 250 Hz, after which the data were re-referenced to the average reference, and filtered offline with a low-pass setting of 125 Hz (notch filter was switched on). The P50 waves were identified and scored as described by Nagamoto et al. (1989): P50 waves elicited by the first (or conditioning) stimulus were identified as the greatest positivity in a window from 40 ms to 90 ms after stimulus presentation. The amplitude was defined as the difference between this peak and the preceding trough. The P50 peaks elicited by the second (or testing) stimulus were defined accordingly, with the further constraint that its peak latency had to lie within the latency of the conditioning peak (±10 ms). P50 suppression was defined as the ratio T/C, where T represents the amplitude to the testing stimulus and C represents the amplitude to the conditioning stimulus.

**Statistical analysis**

All statistical analyses were performed with SPSS for Windows, version 11.0 (SPSS Inc. Chicago, IL, USA). Effect of treatment on startle magnitude was analysed using an ANOVA with the factors ‘treatment’ (placebo or imipramine), ‘order’ (PPI/habituation assessed first or P50 suppression assessed first) and ‘stimtype’ (pulse alone, prepulse-pulse 60 ms/76 dB; prepulse-pulse 120 ms/76 dB; prepulse-pulse 60 ms/85 dB; or prepulse-pulse 120 ms/85 dB). Prepulse inhibition of the startle reflex was analysed using analysis of variance (ANOVA) with the factors ‘treatment’, ‘order’, ‘prepulse intensity’ (76 dB or 85 dB) and SOA (60 ms or 120 ms). Furthermore, since studies of patients with schizophrenia have shown that the largest deficits are observed at SOA = 120 ms and a prepulse intensity of 85 dB (Braff et al., 2001), a planned comparison of PPI at the highest SOA and prepulse intensity in the two treatments was performed with a paired-samples Student’s t test. Habituation was analysed using ANOVA of mean startle amplitude in blocks 1 and 3 with the factors ‘treatment’, ‘order’ and ‘block’ (block 1 or block 3), and in the first four trials of block 1 separately with factors ‘treatment’, ‘order’ and ‘trial’ (trials 1–4).

Similarly to the PPI data, analysis of the P50 suppression data started with an ANOVA with the factors ‘treatment’ and ‘stimtype’ (conditioning or testing stimulus), to find out whether P50 suppression occurred, and to see whether treatment had an effect on raw P50 amplitude. The effect of treatment on P50 suppression was analysed with an ANOVA with the factors ‘treatment’ and ‘order’.
Results

PPI

The ANOVA revealed a significant effect of stimtype \([F(4, 16) = 12.31, \ p < 0.001]\), indicating that PPI occurred. Neither an effect of treatment nor of order was found on raw startle amplitude data. The ANOVA on % PPI showed neither an effect of treatment nor of order or SOA, but did reveal a significant main effect of prepulse intensity, indicating an increased PPI with increasing prepulse intensity (Figure 1).

The planned comparison of % PPI in the prepulse-pulse trials with SOA = 120 ms and prepulse intensity = 85 dB, revealed a significant effect of treatment, PPI being significantly less in the imipramine treatment, when compared to the placebo treatment \((t = 2.51, \ d.f. = 15, \ p < 0.05; \ Figure 1)\). In order to find out whether this effect was due to imipramine affecting the ASR in the pulse-alone trials or in the prepulse-pulse trials an ANOVA with the factors treatment and prepulse intensity (no prepulse or the 120 ms/85 dB prepulse) on the raw startle amplitudes was performed. No interaction effect between treatment and prepulse intensity was found, indicating that the significant effect of the planned comparison on % PPI originates from imipramine non-significantly affecting the ASR in the pulse-alone trials as well as the ASR in the prepulse-trials (decreasing the first and increasing the second).

Habituation

A significant effect of block was found \([F(1, 17) = 17.96, \ p < 0.001]\), indicating that subjects had higher mean startle amplitudes in block 1 than in block 3. Analysis of the first four trials of block 1 revealed a main effect of trial only \([F(3, 15) = 10.85, \ p < 0.001]\). Neither effects of treatment nor of order were found (Figure 2). It should be noted that although the data from Figure 2 suggest a lower amplitude of the first trial (trial 1 of block 1) of the placebo session than the corresponding first trial of the imipramine session, this difference did not reach significance.

P50 suppression

The ANOVA revealed a main effect of pulse, indicating that the subjects’ response elicited by the conditioning stimulus was significantly stronger than the response elicited by the testing (T) stimulus \([F(1, 17) = 38.35, \ p < 0.001]\), indicating that the subjects showed P50 suppression. Neither a treatment main effect, nor a treatment × stimtype second-order interaction was found, indicating no significant effects of imipramine on raw P50 amplitude. However, the paired-samples Student’s t test did reveal a significant effect of treatment on P50 suppression \((t = 2.64, \ d.f. = 17, \ p < 0.05)\), indicating a lower P50 suppression in the imipramine session than in the placebo session (Figure 3). No significant effects of order were found in the P50 data analysis.

Discussion

The aim of the current study was to examine the effects of the dual-acting antidepressant imipramine on sensori(motor) gating (PPI and P50 suppression) and habituation of the startle reflex. Consistent with the hypotheses, imipramine was found to decrease P50 suppression as well as PPI. Habituation was, however, not affected by imipramine.

Most pharmacological studies of PPI are animal studies. As mentioned in the Introduction however, there are conflicting results between human and animal studies, especially regarding monoamines. Serotonin decreases PPI in rats (Geyer et al., 2001) but seems to have either no effect or to increase PPI in humans (Braff et al., 2001). Moreover, there are reports on species-related differences in the binding patterns of imipramine and citalopram (Duncan et al., 1992), and in the neuroanatomical topography of serotonin and \(\alpha_1\) receptors in rats and humans (Duncan et al., 1998; Palacios et al., 1987). Conclusions about the human monoamine system based on animal studies are therefore problematical, which is why results from animal studies will not be discussed further.
To our knowledge, only one other study has examined the effect of dual-acting antidepressants on sensorimotor gating (PPI). Amitriptyline, a tricyclic antidepressant with both noradrenaline- and serotonin-uptake blocking action, significantly decreased the startle magnitude in humans but did not affect PPI (Phillips et al., 2000). In the current study, however, imipramine did not significantly reduce startle magnitude but did decrease % PPI. It is plausible that the differences between both studies were caused by the differences in receptor affinities of the compounds that were used: imipramine has higher affinity for the noradrenergic receptor than amitriptyline (Goodman-Gilman et al., 2001), and therefore will increase noradrenergic activity more, which, in turn, could have resulted in more disruption of PPI. Indeed, desipramine (50 mg), a selective noradrenaline reuptake inhibitor (SNRI), has been shown to decrease PPI in healthy volunteers (Oranje et al., 2004) and Quednow et al. (2004) found a trend of reduced PPI in depressed patients after a 2-wk treatment with another SNRI (8 mg reboxetine). These studies are in line with the above-mentioned notion of a noradrenergic involvement in PPI. However, Phillips et al. (2000) did not find any effect on PPI with a single dose of reboxetine (4 mg) in a group of healthy subjects. These contradictory results might be explained by dose-related differences between the studies, 4 mg reboxetine might have been too low to affect PPI. In a recent study, buspirone, a partial serotonin agonist disrupted PPI (Gogos et al., 2005). However, besides increasing serotonin activity, buspirone has also been reported to increase noradrenergic activity in humans (Lechin et al., 1998), thus one can argue that the PPI reduction was due to increased levels of noradrenaline instead of serotonin. Several studies have investigated the effect of SSRIs on sensorimotor gating, however, none found an effect on PPI (Liechti et al., 2001; Phillips et al., 2000; Quednow et al., 2004), again indicating that it was the noradrenergic activity of imipramine that disrupted PPI in the current study, instead of its serotonergic activity. There are only a few human studies in which the effects on PPI of serotonergic compounds other than SSRIs were investigated: MDMA (Liechti et al., 2001) and psilocybin (Gouzoulis-Mayfrank et al., 1998), both hallucinogenic drugs, were found to improve PPI in healthy subjects. It is probable, however,
that the differences between SSRIs, psilocybin and MDMA on PPI are caused by differences in receptor-binding characteristics. Psilocybin is a 5-HT1A and 5-HT1C receptor agonist (Gouzoulis-Mayfrank et al., 1998) whereas MDMA has a much broader receptor profile including serotonin, dopamine and noradrenaline receptors (Liechti et al., 2001). In summary, it is likely that imipramine in the current study reduced PPI by increasing noradrenergic activity, and not by increasing serotonergic activity.

Similar to the study of Quednow et al. (2004) in which sertraline (a SSRI) reduced habituation, it was anticipated that imipramine would decrease habituation by increasing serotonergic activity. In contrast, however, imipramine showed no effect on habituation, which is consistent with the studies of Liechti et al. (2001) and Gouzoulis-Mayfrank et al. (1998), in which respectively MDMA and psilocybin (both monoaminergic hallucinogenic drugs) did not affect habituation of the startle reflex. Further, Liechti et al. (2001a) found no effect of citalopram (a SSRI) on habituation of the startle reflex. Only one study has investigated the effect of increased noradrenergic activity on habituation. In that study, desipramine (a SNRI) had no effect on habituation (Oranje et al., 2004).

Similar to PPI, imipramine significantly reduced P50 suppression in the current study. In 1994 Adler and colleagues found that yohimbine, a presynaptic α2 antagonist (which increases noradrenergic neuronal transmission in the CNS) decreased P50 suppression in healthy volunteers. In addition, P50 suppression in healthy volunteers was significantly decreased by ayahuasca, a hallucinogenic tea, which binds to the 5-HT1A/1C receptor sites in the CNS (Riba et al., 2002). However ayahuasca, in addition to being a 5-HT1A/1C receptor agonist, also increases the level of noradrenaline (Riba et al., 2003) which makes it conceivable that, similar to the study of Adler et al. (1994), it was the increased noradrenergic activity from ayahuasca that decreased the P50 suppression. These studies indicate that similarly to sensorimotor gating, increased noradrenergic activity decreases sensory gating in healthy volunteers, and therefore suggest that it was the noradrenergic activity of imipramine that decreased P50 suppression in the current study.

Antidepressant medication, added to a continuing dose of antipsychotic medication, is often used in the treatment of negative symptoms or depressive syndromes occurring in the course of schizophrenia. A double-blind, placebo-controlled clinical trial in which psychotic patients were treated with antipsychotics, combined with either desipramine, imipramine or placebo, found more thought disorders in the patient groups receiving the additional antidepressants than in the placebo group; it was suggested that the antidepressants might prolong the recovery of some of the psychotic features of schizophrenia (Kramer et al., 1989). In a study of Kirili et al. (1998) the effect of imipramine and sertraline was compared in a study of post-psychotic schizophrenic patients stable on antipsychotic medication. In the imipramine group 10% of the patients had to be excluded due to aggravation of schizophrenic symptoms whereas no such problem was encountered in the sertraline group. However, the groups were relatively small and the results were not significant. Siris et al. (2000) studied the effect of imipramine and placebo in a group of schizophrenic patients who were stable on antipsychotic medication; they found no differences in psychotic symptoms between the patients receiving imipramine and the patients receiving placebo. In addition, citalopram, added to the antipsychotic medication of a group of stable schizophrenic patients did not alter the level of psychotic symptoms (Friedman et al., 2005). These studies make it likely that it was the increased noradrenergic, and not the increased serotonergic activity that caused the aggravation of psychotic symptoms in the studies of Kramer et al. (1989) and Kirili et al. (1998).

There are some limitations to the current study. Even though sensory gating and sensorimotor gating paradigms are thought of as models for schizophrenia, one cannot draw the conclusion that neurotransmitters that induce gating deficits in healthy volunteers are indeed contributing to the pathology of schizophrenia, but it may indicate what should be investigated further. Another limitation is that participants received only one dose of imipramine. Whether the effect of imipramine on gating will increase with time, like the treatment effect of antidepressant medication, or cease with time, like many of the side-effects of antidepressant medication, cannot be determined by the current study. Similarly, one should be cautious with extrapolating the results of the current study to other psychiatric illnesses in which treatment with antidepressants is necessary (e.g. depression) without further research specifically oriented towards these illnesses. Furthermore, the dual-acting effect of imipramine limits the conclusions that can be drawn from the current study. Future studies should focus on compounds with a more specific monoamine profile.

In conclusion, evidence was found for imipramine to disrupt both sensory gating and sensorimotor gating in healthy volunteers, while it did not affect habituation of the startle reflex. The current study does
not support adjunctive treatment of psychotic depression with dual-acting antidepressants. Future research should focus more specifically towards the serotonergic system targeting compounds, both in healthy humans, and in randomized clinical trials of schizophrenic patients who are treated with these kinds of antidepressants.

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Statement of Interest
None.

References


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