Research Paper

Dexamphetamine widens temporal and spatial binding windows in healthy participants

Faiz M. Kassim, PhD; Samra Krakonja Lahooti, BSc; Elizabeth Ann Keay, BSc; Rajan Iyyalol, MD; Jennifer Rodger, PhD; Matthew A. Albrecht, PhD; Mathew T. Martin-Iverson, PhD

Background: The pathophysiology of psychosis is complex, but a better understanding of stimulus binding windows (BWs) could help to improve our knowledge base. Previous studies have shown that dopamine release is associated with psychosis and widened BWs. We can probe BW mechanisms using drugs of specific interest to psychosis. Therefore, we were interested in understanding how manipulation of the dopamine or catecholamine systems affect psychosis and BWs. We aimed to investigate the effect of dexamphetamine, as a dopamine-releasing stimulant, on the BWs in a unimodal illusion: the tactile funneling illusion (TFI). **Methods:** We conducted a randomized, double-blind, counterbalanced placebo-controlled crossover study to investigate funnelling and errors of localization. We administered dexamphetamine (0.45 mg/kg) to 46 participants. We manipulated 5 spatial (5–1 cm) and 3 temporal (0, 500 and 750 ms) conditions in the TFI. **Results:** We found that dexamphetamine increased funnelling illusion (p = 0.009) and increased the error of localization in a delay-dependent manner (p = 0.03). We also found that dexamphetamine significantly increased the error of localization at 500 ms temporal separation and 4 cm spatial separation ($p_{interaction}$ = 0.009; $p_{500msl4cm\ v.\ baseline}$ = 0.01). **Limitations:** Although amphetamine-induced models of psychosis are a useful approach to understanding the physiology of psychosis related to dopamine hyperactivity, dexamphetamine is equally effective at releasing noradrenaline and dopamine, and, therefore, we were unable to tease apart the effects of the 2 systems on BWs in our study. **Conclusion:** We found that dexamphetamine increases illusory perception on the unimodal TFI in healthy participants, which suggests that dopamine or other catecholamines have a role in increasing tactile spatial and temporal BWs.

Introduction

People integrate multiple stimuli over space and time to form unified percepts of objects and events,[1] and alterations in integration have been proposed as being important for a range of clinical disorders that experience alterations in perception.[2,3] Stimulus binding windows (BWs) reflect the temporal and spatial intervals over which stimuli from multimodal or unimodal sensory systems are to be associated with one another and bound into a single perceptual entity. Values for BWs depend on a variety of parameters: the modalities of the stimuli,[4–6] the order of multimodal stimuli,[4–6] age,[7–10] peripheral sensory loss such as vestibular hypofunction,[11] and psychiatric diagnoses such as psychotic illnesses, autism and attention-deficit/hyperactivity disorder.[3,12–20]

Illusory procedures have been used to investigate body perceptions in people with schizophrenia with passivity symptoms, which are characterized by disturbances in core body representations including body image and body schema.[12–14] People with schizophrenia also have wider BWs, and dopamine is strongly implicated in schizophrenia. Like the experience of touch feel illusion or body ownership illusion in rubber hand illusion (RHI) tests in people with schizophrenia and their offspring,[17,21] administration of dexamphetamine to healthy participants increases illusion strength in RHI and widens temporal BWs.[22] However, the exact role of dopamine in illusory perception and BWs is poorly understood. One way of studying the role of dopamine[23,24] and the relation between dopamine and the illusion in healthy people is to use drugs that increase extracellular dopamine levels and dopamine transmission,[22] as several drug models of schizophrenia have suggested.[25,26] The amphetamine model of schizophrenia is one of the proposed approaches[27–30] that is widely used owing to the known pharmacology, low cost, high availability and well-understood safety profile in humans and animals.[31,32] Amphetamine increases the synaptic levels of monoamines (dopamine, noradrenaline and serotonin) by increasing their release through a reversal of the monoamine transporters, primarily the catecholamine transporters.[33,34] For example, amphetamine increases the synaptic

Correspondence to: F.M. Kassim, The Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Swaziland St, 1000, Addis Ababa, Ethiopia; faiz.mohammed@sphmmc.edu.et/ faizphr@gmail.com.

Submitted Aug. 24, 2022; Revised Sep. 28, 2022; Revised Oct. 25, 2022; Revised Nov. 9, 2022; Accepted Nov. 11, 2022

Cite as: *J Psychiatry Neurosci* 2023 March 14;48(2). doi: 10.1503/jpn.220149

level of dopamine by increasing its release through a reversal of the dopamine transporter.[35,36] Dexamphetamine (D-amphetamine) is more potent than L-amphetamine (3- to 10-fold) or a racemic mixture of L- and D-amphetamine.[37] It can increase dopamine release, making its dopaminergic effects equipotent with its effects on noradrenaline release.[38–40]

Therefore, to characterize the implication of dopamine on tactile funnelling illusion (TFI), we evaluated the effects of dexamphetamine (0.45 mg/kg) on temporal and spatial BWs in a larger sample population of healthy participants than previously used for RHI tests. The TFI is a simple and inexpensive tool to test tactile illusions by manipulating spatial and temporal conditions.[41,42] Therefore, it is an ideal means to test effects of dexamphetamine on both temporal and spatial BWs in the unimodal somatosensory domain, and was chosen for those purposes. We hypothesized that dexamphetamine would increase the experience of unimodal illusory perception and BWs as it previously affected RHI.

Methods

The University of Western Australia (UWA) Human Research Ethics Committee granted ethical approval for this study (RA/4/1/7557). The study is registered at the Australian New Zealand Clinical Trials Registry (ACTRN12615000619549). All 46 participants were recruited via lecture announcements, word of mouth, advertisements on campus notice boards, social media and university group emails. We sent a prospectus package that contained the participant information form, participant consent form, consumer medication information on dexamphetamine and contact information to those who showed interest. We informed participants that they should abstain from any psychoactive substance 24 hours before the test.

We included participants if they were between the ages of 17 and 60 years, and female participants who were not pregnant and who were using contraceptives to avoid pregnancy if they were sexually active and fertile. We excluded participants if they had heart or severe blood vessel disease; high blood pressure (systolic > 140 mm Hg, diastolic > 90 mm Hg); glaucoma; hyperthyroidism; tics (including Tourette syndrome or a family history of Tourette syndrome); sensitivity to dexamphetamine; any degenerative disease of the nervous system; epilepsy or other neurologic disorders, including head injury; psychiatric or psychological problems; a serious medical problem for which they were receiving or had received treatment; substance abuse disorder; a family history of schizophrenia in their first-degree relatives (parents, children or siblings); use of any drug, including alcohol or any illicit drug, within 24 hours of each testing session; used caffeine on the day of testing; had taken prescription medication other than oral contraceptives or acne medication; or used over-the-counter medication in the 48 hours before each testing session.

Participants

We recruited 46 healthy participants (20 female) with a mean (± standard deviation [SD]) age of 22.9 (± 4.7) years and a mean weight of 71.7 (± 14) kg.

Drug and design

We used a randomized, double-blind, counterbalanced placebo-controlled crossover study in which the participant received either dexamphetamine or placebo, in a counterbalanced permuted block randomization (i.e., randomized in sets of 4 consecutive participants) fashion such that there were equal numbers with placebo first and active drug first. We administered dexamphetamine (0.45 mg/kg, taken orally; Aspen Pharmacare, Australia), giving a mean dosage of 32.3 (± 6.2) mg based on the mean weight of the participants of 71.7 kg. Exact same sizes and numbers of capsules containing either placebo (glucose) or dexamphetamine (0.45 mg/kg) were prepared using 1, 2.5, 5 and 10 mg tablets of dexamphetamine sulfate. We selected this dose based on previous studies in healthy participants that showed significant effects on a range of illusory and psychophysiological measures.[22,23,43]

The testing session ran from 9 am to 3 pm over a total of 2 days (with a minimum separation of 1 wk) for each participant. The drug or placebo was administered at 9 am, and then physiologic measurements and demographic data were taken. Transportation and lunch were provided with no additional financial incentive. Informed consent was obtained and, in addition to the exclusion criteria, formal medical and psychiatric assessments by psychiatrists were conducted before the experiment on the first day. We then recorded the demographic information (sex, age and weight).

General procedures

Procedure for tactile funnelling illusion

We administered the TFI test immediately after lunch (i.e., lunch was around 200 min after administration of the drug, and TFI was conducted at about 230 min). Participants completed a separate task (the marble hand illusion) between the psychological tests and TFI. We will analyze and report on the data from this other illusory task separately. The participant was seated and then blindfolded. Their dominant arm was placed on the table with the palm facing the ceiling. For the reference point, a straight line was drawn across the arm 5 cm below the elbow. We started the tests of the tactile (touch) using the compass (caliper) at a distance of 5 cm, then at 1cm reductions to a final spacing of 1 cm (i.e., 5, 4, 3, 2 and 1 cm). There were 5 touches at each distance, and the touch was meant to be light (around 2 mm deep) in areas with less hair. We placed 1 point of the caliber on the reference line and then indented different points on the reference line for 5 touches at each distance (a total of 75 touches per participant per session). There were 3 temporal conditions: 0, 500 and 750 ms (Appendix 1, available at jpn.ca/lookup/doi/10.1503/jpn.220149/tab-related-content). For the 2 asynchronous conditions (500 and 750 ms), the TempoPerfect Metronome software program was used by the examiner as an alarm for the delay between the 2 touches. The order of delays was 750–500–0 ms. We measured funnelling (the number of touches perceived) and error of localization (EL) as outcomes. Funnelling is the awareness aspect of the illusion (if the participant perceived 1 touch instead of 2), whereas EL is the error of spatial localization from the reference line (0 cm).

Psychological scales
We administered the following 3 rating scales once per day (90 min after treatment) during our study: Brief Psychiatric Rating Scale (BPRS),[44] Scale for the Assessment of Positive Symptoms (SAPS)[45] and Magical Ideation Scale (MIS).[46]

Physiologic measures
We recorded blood pressure (BP), heart rate and temporal body temperature (temperature) 5 times each day, in triplicate, to follow the time course of drug and placebo effects on autonomic functioning. We recorded BP and heart rate using an Omron HEM-7121 (RML32) automatic BP monitor (Kyoto, Japan), and body temperature (°C) was recorded using a MedeScan RC008 touchless thermometer (Condell Park, Australia). The consecutive physiologic testing times were 0, 60, 110, 210 and 370 minutes after drug administration.

Statistical analysis

We used R version 3.6.3 (R Core Team 2020), and dply, ez, mblm, lme4, plyr and Rmisc packages to perform the statistical analysis. We used repeated-measures analysis of variance (ANOVA) to analyze the data, with delay, distance and drug condition as within-participants factors and drug order as a between-participants factor.

We inspected plots of the residuals and Q–Q plots to ensure the residuals approximated a normal distribution. We then conducted paired *t* tests for pairwise comparisons between drug and placebo. We used Wilcoxon rank–sum tests with continuity correction if the residuals deviated substantially from normality. Accordingly, we analyzed the TFI of the overall participants using repeated-measures ANOVA with Greenhouse–Geisser corrections if the assumption of sphericity was violated (all degrees of freedom reflect the Greenhouse–Geisser–corrected degrees of freedom where sphericity was violated) and calculated generalized η^2 effect sizes. Each psychological scale was analyzed using Wilcoxon rank–sum tests with continuity correction. All pairwise comparisons are with Bonferroni correction. Exceptions to these methods are listed in the Results.

As a common statistical model, we have taken into consideration the combined effect (i.e., interaction) of 2 or more than 2 variables (e.g., delay and distance) on an outcome (i.e., funnelling or EL). Widaman[47] and Buckless and Ravenscroft[48] suggested that it is preferable to develop statistical methods for testing the relation between dependent and independent variables or for testing ordinal or disordinal interactions. An ordinal interaction has nonsymmetrical patterns of cell means or has "the cross-over of predicted values at the boundary or outside the range of observed values" (e.g., Figure 1A in our case), whereas a disordinal interaction has a symmetric pattern of cell means or has "a cross-over of predicted values within the observed range of values" (e.g., Figure 1C in our case).[47,49] In other words, ordinal interaction presents "when the effect of one factor is in the same direction for each level of the other factor while it may vary in effect size." A disordinal interaction is also called "cross-over interaction" or "double dissociation" and presents "if a factor has opposite effects across at least 2 levels of the other factor."[50] Therefore, it has been suggested that researchers should identify or state the detail of whether they predict ordinal or disordinal interactional effects. We have predicted ordinal interactions. Importantly, an increased number of factors or levels of factors may result in unexpected analytical outputs.[51] Interaction effects identified using ANOVA are more reliable.[52] However, as conventional ANOVA commonly detects main effects and is less powerful for testing ordinal interactions,[48,53] planned comparisons are applied to identify whether there are interaction effects or not.[51,53]

Power analysis
We used the G*Power 3.1 power calculator and based our predicted mean difference (drug–placebo) and SD of the difference on findings in our laboratory on the effect of dexamphetamine on the "embodiment" component of the RHI, with an effect size of 0.43 ($\alpha = 0.5$), with a power of 0.80 (80%) with a 2-tailed test.

Results

Tactile funnelling illusion

We analyzed TFI with 2 outcomes: the number of times 2 touches were perceived as 1 (funnelling) and EL away from the reference line. There were significant main effects of dexamphetamine on funneling ($F_{1,45} = 7.3$, $p = 0.009$, $\eta^2 = 0.008$) but not on EL ($F_{1,45} = 0.65$, $p = 0.43$, $\eta^2 = 0.001$) (Appendix 1). However, as shown in Figure 1, we found significant interactions between drug and delay on EL ($F_{1.4,63} = 3.7$, $p = 0.03$, $\eta^2 = 0.0052$) but not on funnelling ($F_{2,90} = 0.14$, $p = 0.87$, $\eta^2 = 0.00001$). There were also no significant interactions between drug and distance ($F_{4,180} = 0.92$, $p = 0.45$, $\eta^2 = 0.0013$), and drug, distance and delay ($F_{8,360} = 0.3$, $p = 0.96$, $\eta^2 = 0.0007$) on funnelling. For EL, we found no significant interactions between drug and distance ($F_{4,180} = 0.92$, $p = 0.45$, $\eta^2 = 0.0013$) or drug, distance and delay ($F_{8,360} = 1$, $p = 0.36$, $\eta^2 = 0.0037$).

We also found significant main effects of delay ($F_{1.12,50.4} = 30$, $p < 0.0001$, $\eta^2 = 0.29$) and distance ($F_{2.1,95.4} = 77.41$, $p < 0.0001$, $\eta^2 = 0.33$) on funnelling, and a significant effect of delay ($F_{1.3,60} = 25.3$, $p < 0.00001$, $\eta^2 = 0.087$) and distance on EL ($F_{2.7,124} = 5.45$, $p = 0.0001$, $\eta^2 = 0.027$), which show that increasing either the delay or distance condition decreases funnelling illusion (Figure 1). Consistent with a spatiotemporal interaction on illusory perception that showed that increasing both delay and distance condition decreases illusion, we found significant interactions between delay and distance on EL ($F_{3,270} = 5.16$, $p = 0.00001$, $\eta^2 = 0.03$). However, there were no significant interactions between delay and distance on funnelling ($F_{8,360} = 1.4$, $p = 0.19$, $\eta^2 = 0.0045$).

We also found significant drug effects on EL at specific delay (500 ms) and distance (4 cm) conditions, showing that dexamphetamine increases temporal and spatial BWs, respectively (Figure 2).

Psychological measures

Table 1 presents the effect of dexamphetamine and placebo on each psychological scale. The Wilcoxon rank–sum test with continuity correction showed that dexamphetamine significantly increases BPRS ($V = 767$, $p = 0.0000001$), MIS ($V = 441$, $p = 0.0008$) and SAPS ($V = 552$, $p = 0.00009$).

Physiologic measures

Physiologic data from 1 participant were missing, leaving data for 45 participants for our analysis. Analysis of variance showed that there were significant main effects of dexamphetamine on diastolic BP ($F_{1,44} = 122.6$, $p < 0.0001$, $\eta^2 = 0.18$), systolic BP ($F_{1,44} = 78.02$, $p < 0.0001$, $\eta^2 = 0.15$), temperature ($F_{1,44} = 4.7$, $p = 0.03$, $\eta^2 = 0.02$) and heart rate ($F_{1,44} = 48.14$, $p < 0.0001$, $\eta^2 = 0.13$). There were significant interactions between drug and time on diastolic BP ($F_{3.2,140.8} = 22.6$, $p < 0.0001$, $\eta^2 = 0.09$), systolic BP ($F_{2,88} = 4.72$, $p = 0.00018$, $\eta^2 = 0.05$), temperature ($F_{3.1,132.7} = 3.3$, $p = 0.0036$, $\eta^2 = 0.023$) and heart rate ($F_{3.3,144.3} = 29.4$, $p < 0.0001$, $\eta^2 = 0.14$) (Figure 3).

Discussion

We investigated the role of dopamine or catecholamines on tactile BWs by administering dexamphetamine (0.45 mg/kg) to healthy participants undergoing the TFI. Our findings were as follows: dexamphetamine increased the funnelling (the awareness aspect of the illusion) strength, but the results failed to show evidence of widened delay or spatial BWs for funnelling because there were no temporal or spatial condition–dependent changes in the funnelling illusion relative to placebo; dexamphetamine increased the EL at the 500 ms asynchronous delay condition, which indicated widened temporal BWs; and dexamphetamine increased EL illusion specifically at 4 cm, which indicated widened spatial

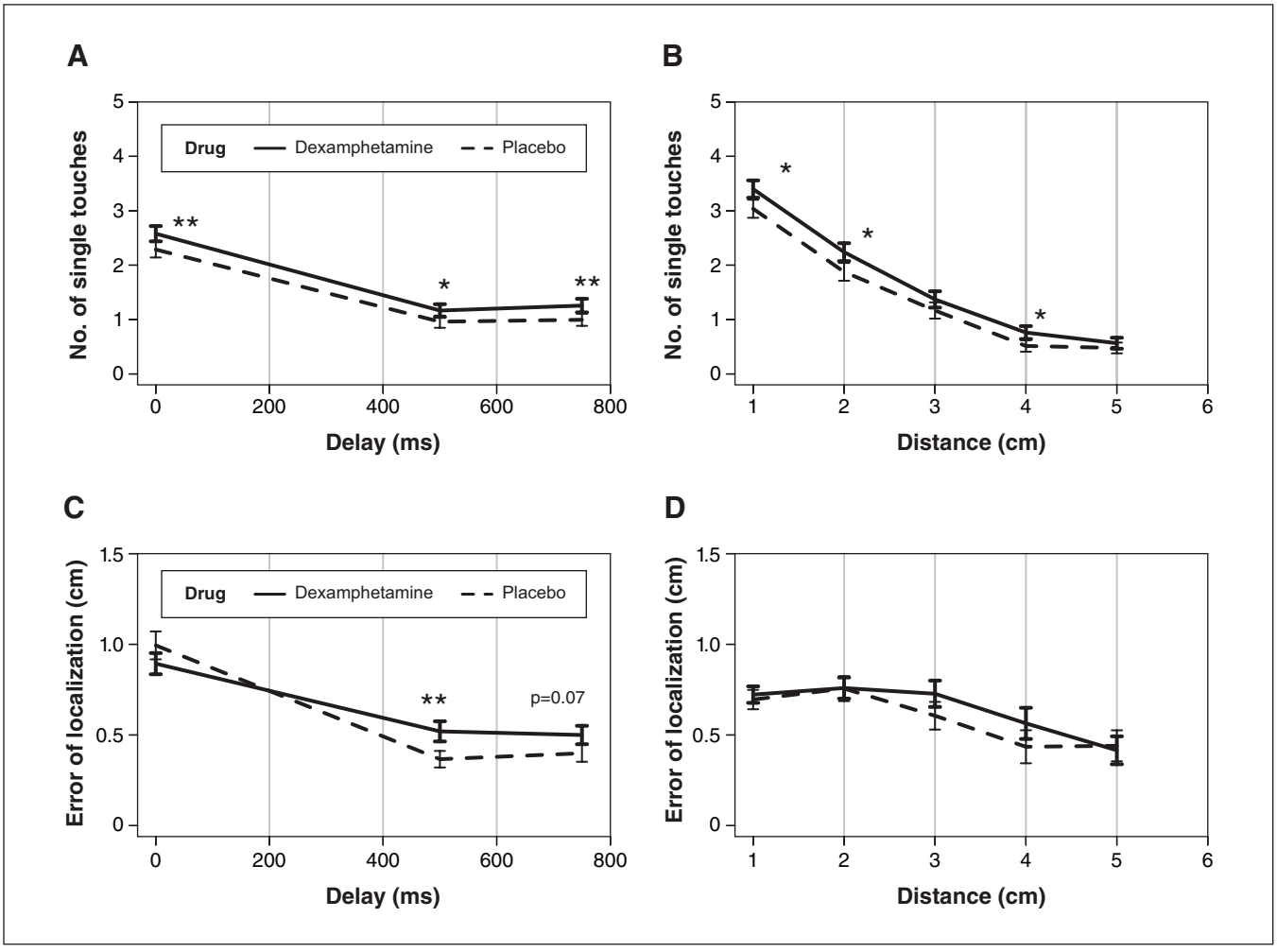

Fig. 1: Effects of dexamphetamine (0.45 mg/kg, administered orally) on (A and B) funnelling and (C and D) error of localization (EL) versus (A and C) delay conditions or (B and D) distance conditions. Data are presented as numbers of 1 touch (single touches felt) versus (A) delay or (B) distance for funnelling; EL versus (C) delay or (D) distance. Although there was a significant interaction of only drug and delay on EL across (C) delay, pairwise comparisons indicated that there were significant effects of dexamphetamine on (A and B) funnelling across (A) each delay condition and (B) some distance conditions. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

BWs. Overall, our findings show that dexamphetamine widens spatial and temporal BWs. The effect of dexamphetamine on BWs in the TFI in our study is in agreement with the increase in the visuo-tactile RHI test in healthy participants after receiving dexamphetamine that was reported in a 2011 study,[22] and in projected hand illusion (PHI) or RHI tests that showed people with schizophrenia experienced increased illusion under asynchronous delay conditions.[13,21,54–56]

A 2011 double-blind, placebo-controlled crossover study showed that dexamphetamine increased embodiment during the RHI for both synchronous and asynchronous stimulation in healthy participants.[22] Like this RHI study,[22] we found an increase in temporal BWs after administration of dexamphetamine. We also found that dexamphetamine increased spatial BWs in the TFI. Our findings and those of previous studies in schizophrenia[21,54] or that used dopaminergic agents in healthy participants[22] that reported widening of temporal BWs on multimodal illusions may be linked to increased dopamine.

Various illusion tests have shown that people with schizophrenia experience more illusion in PHI,[12–14] in RHI,[21,54] and in auditory, visual or audiovisual[55] than healthy controls. For instance, Graham and colleagues[56] reported that asynchronous stroking of the hand at 500 ms in people with schizophrenia produced more illusion in PHI. This supports the idea that dexamphetamine-induced increases in dopamine transmission are representative of results expected to be observed in people with schizophrenia.

However, the exact role of dopamine in illusory perception and BWs is poorly understood but may involve modulating activity of the temporoparietal junction. The merging of stimuli into a perception of a unified object or event has been proposed to result from activity in the temporoparietal junction.[57–59] The mesocorticolimbic pathway may modulate activity in the temporoparietal junction via dopamine release in the frontal cortex, which has connections with the temporoparietal junction.[60] Importantly, a 2013 review of positron emission tomography and single-photon-emission computed tomography studies clearly showed that dopamine influences psychosis through mesocorticolimbic and nigrostriatal dopaminergic pathways.[61] Some studies that reviewed spatial learning showed that dopaminergic projections from these circuits influence spatial information (such as sensory or proprioceptive) in the hippocampus.[62,63] It has also been suggested that the somatosensory receptive field in the cortex might be responsible for binding of tactile information,[64] which is also influenced by temporal and spatial variations.[65] These cortex areas might also be a target area for the dopaminergic influence of the tactile BWs.

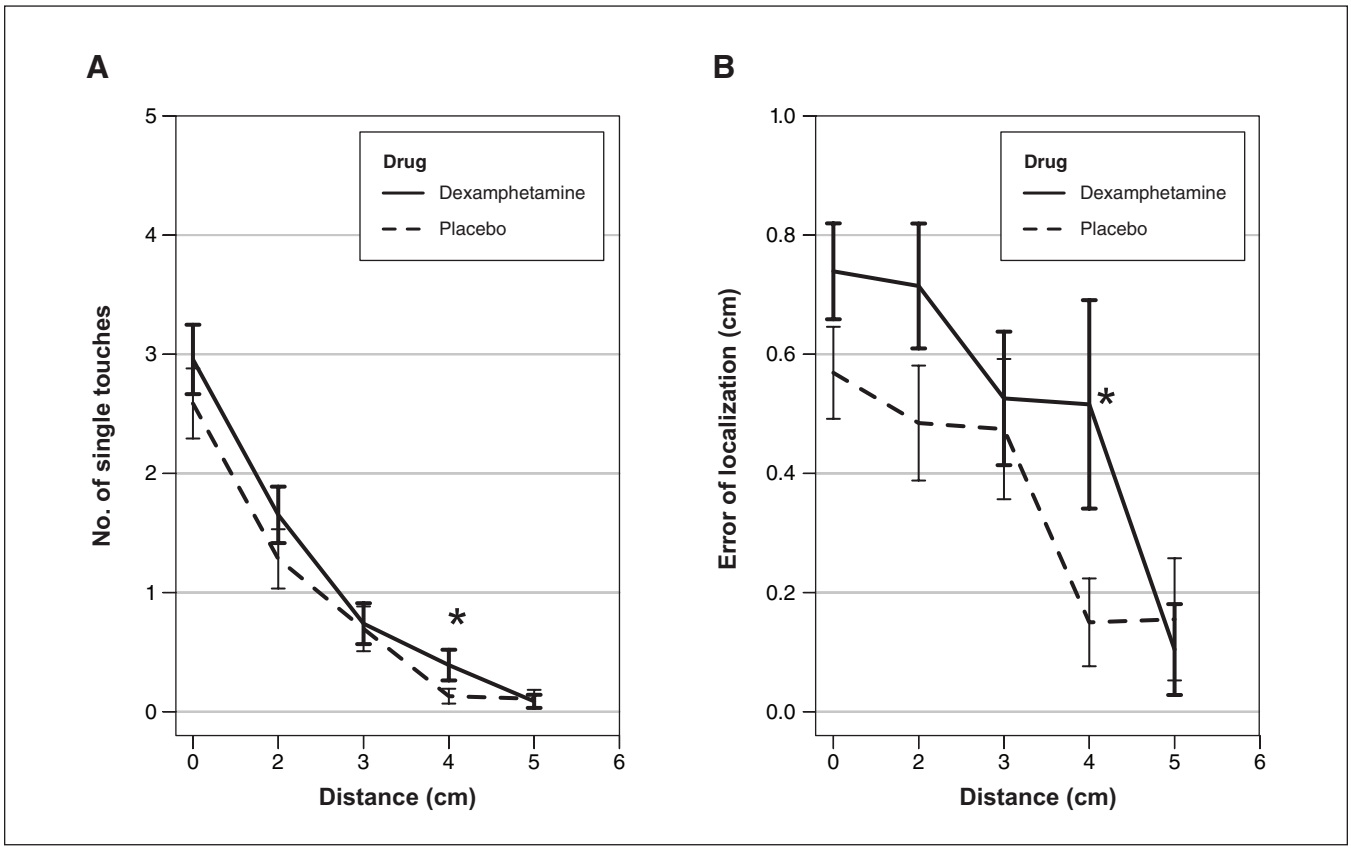

Fig. 2: The effect of dexamphetamine (0.45 mg/kg, administered orally) on (A) funnelling and (B) error of localization (EL) across 500 ms. Data are presented as (A) number of single touches or (B) EL versus distance across 500 ms. Illusion outcomes of dexamphetamine and placebo are significantly different from each other on the funnelling and EL across delay and distance conditions at 500 ms and 4 cm ($p < 0.05$ for both), although the interaction between delay and drug is significant only for EL.

Animal studies have shown that cortical[66,67] and subcortical areas [68–70] are responsible for processing the cortical binding of tactile stimuli presented at similar or different modalities on different skin sites. For example, during synchronous stimulation of fingers, the recorded cerebral potential was less than the simple addition of the potential produced after stimulation of individual fingers.[64,69]

We further found that dexamphetamine increased the funnelling effect, although it failed to expand BWs for the funnelling effect. Previous studies have suggested that "afferent-induced inhibition" causes funnelling illusion,[41,71,72] which may show that dexamphetamine strengthens the afferent-induced inhibition process in the tactile neuron.[68,69] The effect of dexamphetamine on the BWs of EL (without affecting the BWs of funnelling) may indicate that the spatial localization of the single touches felt are dependent more on the internal body schema or map than is the funnelling (awareness of the number of touches) in the absence of visual cues. This further shows that the conscious awareness of sensory processing (e.g., touch perception) is not well mapped into the unconscious body schema (superficial schema or body form representation), which depends on somatosensory and visual

Table 1: Psychological effects of dexamphetamine and placebo

	Score, mean ± SD	
Rating scale	Dexamphetamine	Placebo
BPRS	26.4 ± 4.2*	23.5 ± 1.1
MIS	4.7 ± 7.4*	3.5 ± 5.9
SAPS	4.5 ± 6.3*	2.9 ± 4.9

BPRS = Brief Psychiatric Rating Scale; MIS = Magical Ideation Scale; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation.
*Significant at $p < 0.001$.

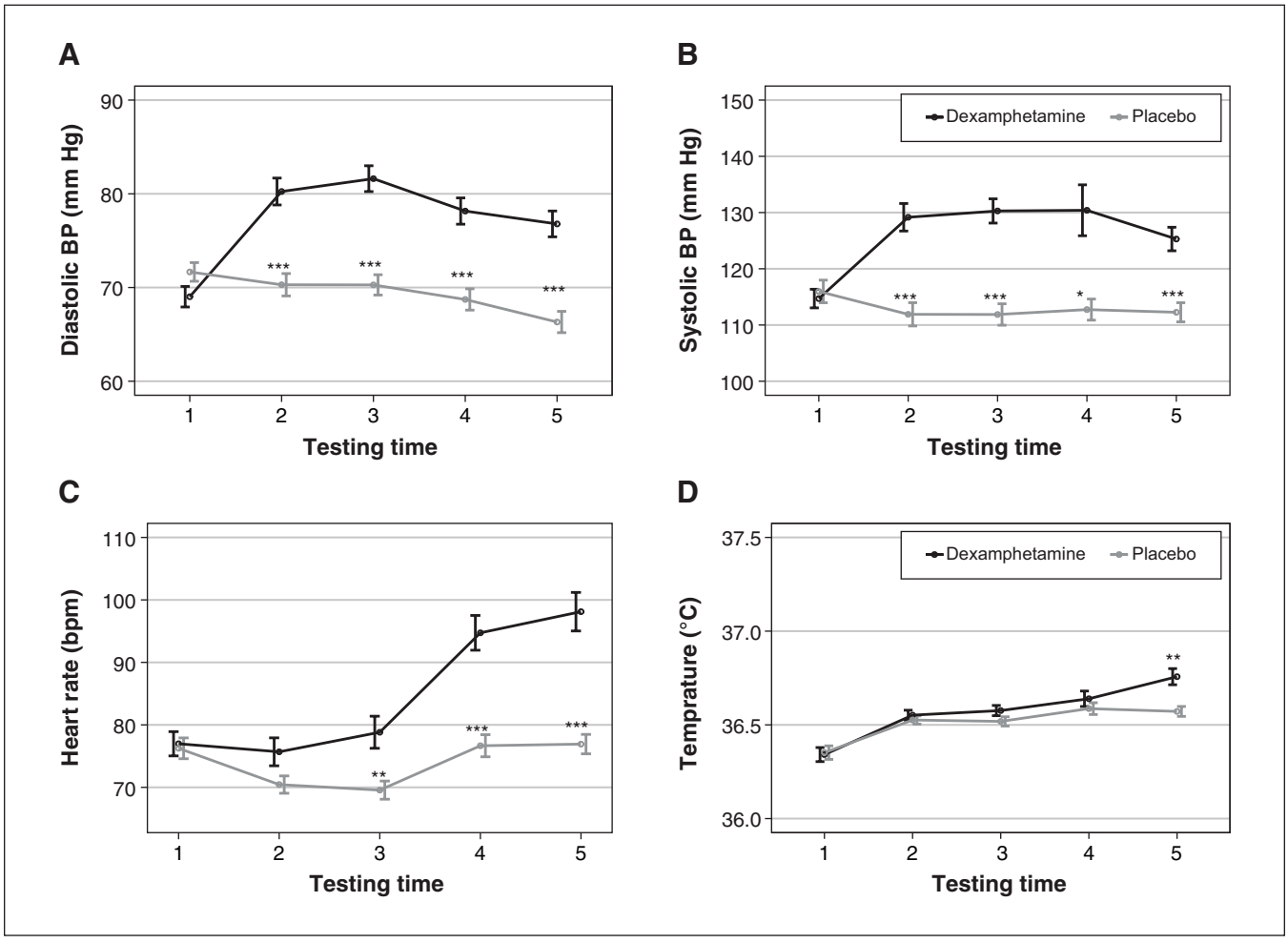

Fig. 3: The effect of dexamphetamine (0.45 mg/kg, administered orally) on (A) diastolic blood pressure (BP), (B) systolic BP, (C) heart rate and (D) body temperature as a function of time. Relative to the placebo, dexamphetamine significantly raised both (A) diastolic BP and (B) systolic BP at the 4 testing times after drug administration (2–5). Dexamphetamine significantly raised (C) heart rate and (D) temperature at 3 (3–5) and 1 (5) testing times after administration, respectively. The peak effect of dexamphetamine on diastolic BP was at measurement time 3, whereas it was at times 3 and 4 for systolic BP. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The 5 testing times were 0, 60, 110, 210 and 370 minutes after drug administration.

inputs, and is involved with tracking and predicting body parts that allows localization of tactile perception.[73–75]

Further research should be done to explore the relation between dopamine or catecholamines and BWs. Our finding may explain that the increased amount of catecholamines by dexamphetamine is sufficient to increase the experience of the TFI and increase BWs. These results also show that the TFI is sensitive to both temporal and spatial conditions that can be further influenced by drugs. The spatial limits showed a nonlinear relation in the strength of EL, which was similar to a previous study that applied 6 spatial positions (17.5–67.5 cm) during RHI tests and reported that a significant nonlinear relation in the strength of the illusion.[76] It has been shown that RHI is sensitive to spatial domain (match/mismatch)[77] and temporal condition.[78] Albrecht and colleagues[22] reported that dexamphetamine increased the embodiment score (mainly the ownership one) during both synchronous and asynchronous conditions. In a self-face recognition test, enfacement illusion was also strong under synchronous delay conditions.[78–80] Similar to our study, Kahrimanovic and colleagues[65] reported that synchronous stimulation of fingers during a tactile experiment caused assimilation effect, whereby there was a high probability of integrating 2 or more simulations as 1. For the TFI, the upper limit of the temporal BWs was reached at the 500 ms delay condition; we suggest that future research target shorter delay conditions to identify the lower bounds of the window. Finally, the present effect of dexamphetamine on spatial and temporal BWs may add to the existing dopamine hypothesis of schizophrenia, although the important drawbacks of using D-amphetamine precludes the degree of association. The disadvantages of the D-amphetamine model of schizophrenia are the complex nature of schizophrenia that could not be mimicked or explained by psychosis induced by D-amphetamine and the nonselective release of monoamines after D-amphetamine administration.[25,26,30,31,81,82]

The important strengths of our study were its design and use of the temporal and spatial conditions to evaluate BWs. We recruited 46 participants, more than double the number of participants in previous dexamphetamine studies on BWs.[22,83] Importantly, our previous TFI study involving 20 healthy participants showed that, although dexamphetamine influenced funnelling illusion based on changes in psychometric score, it failed to modify BWs.[83]

We manipulated and compared the illusory and psychological effects of dexamphetamine at a moderate dose (about 33 mg), which was 2–3 times higher than that used in most previous dexamphetamine challenge studies. We involved participants whose ages and education levels were very close, which provided a homogeneous population and avoided or decreased age-related cognitive differences.[84–88]

There are, however, some important limitations to be noted. We did not measure plasma levels of dexamphetamine to correlate the plasma concentration of dexamphetamine with BWs. However, we conducted the TFI measurement within about 30 minutes of the expected peak concentration of dexamphetamine (i.e., the study was conducted at 230 min). Previous studies have shown that peak plasma concentrations of 0.4–0.5 mg/kg after dexamphetamine administration occur around 180–240 minutes[89–91] and decrease to 75% of the maximum level after 500 minutes.[89] Asghar and colleagues[89] and Silber and colleagues[92] found that the psychological, physiologic or cognitive performance changes did not predict the time course of plasma levels of dexamphetamine. In addition, the half-life of dexamphetamine is about 12 hours, which allows the drug to be active during all psychological or cognitive measurements as shown by the physiologic measurements conducted before and after the TFI. Another limitation is related to the neurochemical model and interpretation. Dexamphetamine induces the release of other neurotransmitters such as noradrenaline[93] and, to a much lesser extent, serotonin,[94] both of which may affect BWs. Therefore, the inferences drawn from our findings may be confounded because noradrenaline pathways or the interaction between dopaminergic and noradrenergic pathways could be an alternative explanation for the effects of dexamphetamine.[26,30,82] Further studies could use selective dopaminergic agents to isolate the effects of dopamine or noradrenaline on BWs. We did not verify abstinence from other psychoactive substances by urine screening, although a previous validation study in our laboratory showed that self-reports regarding recent substance use (e.g., cannabis, within 24 h) were consistent and valid (κ = 0.91).[95]

Conclusion

We have shown that increasing catecholamine release through the administration of dexamphetamine (0.45 mg/kg) increases temporal and spatial BWs in the unimodal funnelling illusion. Further studies using selective dopaminergic and noradrenergic agents will be needed to elucidate whether the observed dexamphetamine effects are driven by dopamine release specifically, as dexamphetamine releases catecholamine.

Affiliations: From the Department of Psychiatry, St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia (Kassim); the Psychopharmacology Unit, School of Biomedical Sciences, University of Western Australia, Perth, WA, Australia (Kassim, Lahooti, Keay, Martin-Iverson); the Psychiatry, Graylands Hospital, Mt Claremont, Perth, WA, Australia (Iyyalol); the Experimental and Regenerative Neurosciences, School of Biological Sciences, University of Western Australia, Crawley, WA, Australia (Rodger); the Brain Plasticity Group, Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia (Rodger); the Western Australian Centre for Road Safety Research, School of Psychological Science, University of Western Australia, Perth, WA, Australia (Albrecht).

Acknowledgment: The authors thank all volunteers for their participation, and all colleagues who assisted in the data collection.

Competing interests: Mathew Martin-Iverson has received payments for expert testimony from the courts of Australia. No other competing interests were declared.

Clinical trials registry: ACTRN12615000619549

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1. Stein BE, Stanford TR. Multisensory integration: current issues from the perspective of the single neuron. *Nat Rev Neurosci* 2008; 9:255-66.
2. Wallace MT, Stevenson RA. The construct of the multisensory temporal binding window and its dysregulation in developmental disabilities. *Neuropsychologia* 2014;64:105-23.
3. Noel JP, Stevenson RA, Wallace MT. Atypical audiovisual temporal function in autism and schizophrenia: similar phenotype, different cause. *Eur J Neurosci* 2018;47:1230-41.
4. Noel JP, Modi K, Wallace MT, et al. Audiovisual integration in depth: multisensory binding and gain as a function of distance. *Exp Brain Res* 2018;236:1939-51.
5. Stevenson RA, Fister JK, Barnett ZP, et al. Interactions between the spatial and temporal stimulus factors that influence multisensory integration in human performance. *Exp Brain Res* 2012a;219: 121-37.
6. Foucher JR, Lacambre M, Pham BT, et al. Low time resolution in schizophrenia Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophr Res* 2007;97:118-27.
7. Graham KT, Martin-Iverson MT, Waters FA. Intentional binding or perceptual repulsion? Binding in a general population sample decreases with age and increases with psychosis-like experiences. *Psychology of Consciousness: Theory, Research and Practice* 2015;2: 269-82.
8. Cowie D, Makin TR, Bremner AJ. Children's responses to the rubber-hand illusion reveal dissociable pathways in body representation. *Psychol Sci* 2013;24:762-9.
9. Bremner AJ, Hill EL, Pratt M, et al. Bodily illusions in young children: developmental change in visual and proprioceptive contributions to perceived hand position. *PLoS One* 2013;8:e51887.
10. Tajadura-Jiménez A, Valjamae A, Asutay E, et al. Embodied auditory perception: the emotional impact of approaching and receding sound sources. *Emotion* 2010;10:216-29.
11. Shayman CS, Seo JH, Oh Y, et al. Relationship between vestibular sensitivity and multisensory temporal integration. *J Neurophysiol* 2018;120:1572-7.
12. Graham-Schmidt KT, Martin-Iverson MT, Holmes NP, et al. Body representations in schizophrenia: an alteration of body structural description is common to people with schizophrenia while alterations of body image worsen with passivity symptoms. *Cogn Neuropsychiatry* 2016;21:354-68.
13. Graham KT, Martin-Iverson MT, Holmes NP, et al. Deficits in agency in schizophrenia, and additional deficits in body image, body schema, and internal timing, in passivity symptoms. *Front Psychiatry* 2014;5:126.
14. Graham-Schmidt KT, Martin-Iverson MT, Waters FAV. Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. *Schizophr Res* 2018;192:75-81.
15. Haβ K, Sinke C, Reese T, et al. Enlarged temporal integration window in schizophrenia indicated by the double-flash illusion. *Cogn Neuropsychiatry* 2017;22:145-58.
16. Klaver M, Dijkerman HC. Bodily Experience in schizophrenia: factors underlying a disturbed sense of body ownership. *Front Hum Neurosci* 2016;10:305.
17. Prikken M, van der Weiden A, Baalbergen H, et al. Multisensory integration underlying body-ownership experiences in schizophrenia and offspring of patients: a study using the rubber hand illusion paradigm. *J Psychiatry Neurosci* 2019;44:177-84.
18. Rossetti I, Romano D, Florio V, et al. Defective embodiment of alien hand uncovers altered sensorimotor integration in schizophrenia. *Schizophr Bull* 2020;46:294-302.
19. Zhou HY, Cai XL, Weigl M, et al. Multisensory temporal binding window in autism spectrum disorders and schizophrenia spectrum disorders: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2018;86:66-76.
20. Panagiotidi M, Overton PG, Stafford T. Multisensory integration and ADHD-like traits: evidence for an abnormal temporal integration window in ADHD. *Acta Psychol (Amst)* 2017;181:10-7.
21. Peled A, Ritsner M, Hirschmann S, et al. Touch feel illusion in schizophrenic patients. *Biol Psychiatry* 2000;48:1105-8.
22. Albrecht MA, Martin-Iverson MT, Price G, et al. Dexamphetamine effects on separate constructs in the rubber hand illusion test. *Psychopharmacology (Berl)* 2011;217:39-50.
23. Woodward ND, Cowan RL, Park S, et al. Correlation of individual differences in schizotypal personality traits with amphetamine-induced dopamine release in striatal and extrastriatal brain regions. *Am J Psychiatry* 2011;168:418-26.
24. Mohr C, Ettinger U. An Overview of the Association between Schizotypy and Dopamine. *Front Psychiatry* 2014;5:184.
25. Steeds H, Carhart-Harris RL, Stone JM. Drug models of schizophrenia. *Ther Adv Psychopharmacol* 2015;5:43-58.
26. Snyder SH. Catecholamines in the brain as mediators of amphetamine psychosis. *Arch Gen Psychiatry* 1972;27:169-79.
27. Angrist B, Sathananthan G, Wilk S, et al. Amphetamine psychosis: behavioral and biochemical aspects. *J Psychiatr Res* 1974;11:13-23.
28. Bell DS. The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 1973;29:35-40.
29. Connell PH. Amphetamine Psychosis. *BMJ* 1957;1:582.
30. Snyder SH. Amphetamine psychosis: a "model" schizophrenia mediated by catecholamines. *Am J Psychiatry* 1973;130:61-7.
31. Białon M, Wasik A. Advantages and limitations of animal schizophrenia models. *Int J Mol Sci* 2022;23:5968.
32. Hermens DF, Lubman DI, Ward PB, et al. Amphetamine psychosis: a model for studying the onset and course of psychosis. *Med J Aust* 2009;190(S4):S22-5.
33. Hutson PH, Tarazi FI, Madhoo M, et al. Preclinical pharmacology of amphetamine: implications for the treatment of neuropsychiatric disorders. *Pharmacol therapeutics* 2014;143:253-64.
34. Kuczenski R, Segal DS, Cho AK, et al. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. *J Neurosci* 1995;15:1308-17.
35. Fleckenstein AE, Volz TJ, Riddle EL, et al. New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol* 2007;47:681-98.
36. Schmitz Y, Lee CJ, Schmauss C, et al. Amphetamine distorts stimulation-dependent dopamine overflow: effects on D2 autoreceptors, transporters, and synaptic vesicle stores. *J Neurosci* 2001;21:5916-24.
37. Parkes JD, Fenton GW. Levo(–) amphetamine and dextro(+) amphetamine in the treatment of narcolepsy. *J Neurol Neurosurg Psychiatry* 1973;36:1076-81.
38. Heal DJ, Smith SL, Gosden J, et al. Amphetamine, past and present — a pharmacological and clinical perspective. *J Psychopharmacol* 2013;27:479-96.
39. Sitte HH, Freissmuth M. Amphetamines, new psychoactive drugs and the monoamine transporter cycle. *Trends Pharmacol Sci* 2015;36:41-50.
40. Easton N, Steward C, Marshall F, et al. Effects of amphetamine isomers, methylphenidate and atomoxetine on synaptosomal and synaptic vesicle accumulation and release of dopamine and noradrenaline in vitro in the rat brain. *Neuropharmacology* 2007;52:405-14.
41. v. Békésy G. Funneling in the nervous system and its role in loudness and sensation intensity on the skin. *Journal of the Acoustical Society of America* 1958;30:399-412.
42. Hayward V. A brief taxonomy of tactile illusions and demonstrations that can be done in a hardware store. *Brain Res Bull* 2008;75:742-52.
43. Graham-Schmidt KT, Martin-Iverson MT, Waters FAV. Setting the beat of an internal clock: Effects of dexamphetamine on different interval ranges of temporal processing in healthy volunteers. *PsyCh J* 2019;8:90-109.
44. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep* 1962;10:799-812.
45. Andreasen N. Scale for the assessment of positive symptoms (SAPS). Iowa City.: University of Iowa; 1984.
46. Eckblad M, Chapman LJ. Magical ideation as an indicator of schizotypy. *J Consult Clin Psychol* 1983;51:215-25.
47. Widaman KF, Helm JL, Castro-Schilo L, et al. Distinguishing ordinal and disordinal interactions. *Psychol Methods* 2012;17:615-22.

48. Buckless FA, Ravenscroft SP. Contrast coding: a refinement of ANOVA in behavioral analysis. *Account Rev* 1990;65:933-45.
49. Suh I, Masli A, Sweeney JT. Do management training grounds reduce internal auditor objectivity and external auditor reliance? The influence of family firms. *J Bus Ethics* 2021;173:205-27.
50. Kuhlmann BG, Erdfelder E, Moshagen M. Testing Interactions in multinomial processing tree models. *Front Psychol* 2019;10:2364.
51. Bobko P. A solution to some dilemmas when testing hypotheses about ordinal interactions. *J App Psych* 1986;71:323-6.
52. Nieuwenhuis S, Forstmann BU, Wagenmakers E-J. Erroneous analyses of interactions in neuroscience: a problem of significance. *Nat Neurosci* 2011;14:1105-7.
53. Strube MJ, Bobko P. *Testing hypotheses about ordinal interactions: Simulations and further comments*. *J App Psych* 1989;74:247-52.
54. Thakkar KN, Nichols HS, McIntosh LG, et al. Disturbances in body ownership in schizophrenia: evidence from the rubber hand illusion and case study of a spontaneous out-of-body experience. *PLoS One* 2011;6:e27089.
55. Williams LE, Light GA, Braff DL, et al. Reduced multisensory integration in patients with schizophrenia on a target detection task. *Neuropsychologia* 2010;48:3128-36.
56. Graham KT, Martin-Iverson MT, Holmes NP, et al. The projected hand illusion: component structure in a community sample and association with demographics, cognition, and psychotic-like experiences. *Atten Percept Psychophys* 2015;77:207-19.
57. Eddy CM. The junction between self and other? Temporo-parietal dysfunction in neuropsychiatry. *Neuropsychologia* 2016;89:465-77.
58. Ricciardi E, Bonino D, Gentili C, et al. Neural correlates of spatial working memory in humans: a functional magnetic resonance imaging study comparing visual and tactile processes. *Neuroscience* 2006;139:339-49.
59. Bonino D, Ricciardi E, Sani L, et al. Tactile spatial working memory activates the dorsal extrastriate cortical pathway in congenitally blind individuals. *Arch Ital Biol* 2008;146:133-46.
60. Mesulam MM, Geschwind N. On the possible role of neocortex and its limbic connections in the process of attention and schizophrenia: clinical cases of inattention in man and experimental anatomy in monkey. *J Psychiatr Res* 1978;14:249-59.
61. Brunelin J, Fecteau S, Suaud-Chagny M-F. Abnormal striatal dopamine transmission in schizophrenia. *Curr Med Chem* 2013;20:397-404.
62. Khamassi M, Humphries MD. Integrating cortico-limbic-basal ganglia architectures for learning model-based and model-free navigation strategies. *Front Behav Neurosci* 2012;6:79.
63. Retailleau A, Boraud T. The Michelin red guide of the brain: role of dopamine in goal-oriented navigation. *Front Syst Neurosci* 2014;8:32.
64. Gandevia SC, Burke D, Mckeon BB. Convergence in the somatosensory pathway between cutaneous afferents from the index and middle fingers in man. *Exp Brain Res* 1983;50:415-25.
65. Kahrimanovic M, Bergmann Tiest WM, Kappers AM. Context effects in haptic perception of roughness. *Exp Brain Res* 2009;194:287-97.
66. Rosén I, Asanuma H. Peripheral afferent inputs to the forelimb area of the monkey motor cortex: input-output relations. *Exp Brain Res* 1972;14:257-73.
67. Zarzecki P, Blum PS, Bakker DA, et al. Convergence of sensory inputs upon projection neurons of somatosensory cortex — vestibular, neck, head, and forelimb inputs. *Exp Brain Res* 1983;50:408-14.
68. Bystrzycka E. BS NA, Rowe M. Inhibition of cuneate neurones: its afferent source and influence on dynamically sensitive "tactile" neurones. *J Physiol* 1977;268:251-70.
69. Ferrington DG, Rowe M. Differential contributions to coding of cutaneous vibratory information by cortical somatosensory areas I and II. *J Neurophysiol* 1980;43:310-31.
70. Tracey DJ. The projection of joint receptors to the cuneate nucleus in the cat. *J Physiol* 1980;305:433-49.
71. Ferrington DG, Nail BS, Rowe M. Human tactile detection thresholds – modification by inputs from specific tactile receptor classes. *J Physiol* 1977;272:415-33.
72. Gardner EP, Spencer WA. Sensory funneling. 1. Psychophysical observations of human subjects and responses of cutaneous mechanoreceptive afferents in cat to patterned skin stimuli. *J Neurophysiol* 1972;35:925.
73. Graziano MSA, Webb TW. The attention schema theory: a mechanistic account of subjective awareness. *Front Psychol* 2015;6:500.
74. Olcese U, Oude Lohuis MN, Pennartz CMA. Sensory processing across conscious and nonconscious brain states: from single neurons to distributed networks for inferential representation. *Front Syst Neurosci* 2018;12:49.
75. Medina J, Coslett HB. From maps to form to space: touch and the body schema. *Neuropsychologia* 2010;48:645-54.
76. Lloyd DM. Spatial limits on referred touch to an alien limb may reflect boundaries of visuo-tactile peripersonal space surrounding the hand. *Brain Cogn* 2007;64:104-9.
77. Costantini M, Haggard P. The rubber hand illusion: sensitivity and reference frame for body ownership. *Conscious Cogn* 2007;16:229-40.
78. Tsakiris M, Haggard P. The rubber hand illusion revisited: visuotactile integration and self-attribution. *J Exp Psychol Hum Percept Perform* 2005;31:80-91.
79. Sforza A, Bufalari I, Haggard P, et al. My face in yours: visuotactile facial stimulation influences sense of identity. *Soc Neurosci* 2010;5:148-62.
80. Tajadura-Jiménez A, Longo MR, Coleman R, et al. The person in the mirror: using the enfacement illusion to investigate the experiential structure of self-identification. *Conscious Cogn* 2012;21:1725-38.
81. Bramness JG, Gundersen ØH, Guterstam J, et al. Amphetamine-induced psychosis — A separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry* 2012;12:221.
82. Kokkinidis L, Anisman H. Amphetamine psychosis and schizophrenia: a dual model. *Neurosci Biobehav Rev* 1981;5:449-61.
83. Kassim FM, Lim JHM, Albrecht MA, et al. Dexamphetamine influences funneling illusion based on psychometric scores. *Human Psychopharmacol Clin Exp*. In press.
84. Salthouse TA, Babcock RL. Decomposing adult age differences in working memory. *Dev Psychol* 1991;27:763-76.
85. Salthouse TA, Babcock RL, Shaw RJ. Effects of adult age on structural and operational capacities in working memory. *Psychol Aging* 1991;6:118-27.
86. Babcock RL, Salthouse TA. Effects of increased processing demands on age differences in working memory. *Psychol Aging* 1990;5:421-8.
87. Grégoire J, Van der Linden M. Effects of age on forward and backward digit spans. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 1997;4:140-9.
88. Hester RL, Kinsella GJ, Ong B. Effect of age on forward and backward span tasks. *J Int Neuropsychol Soc* 2004;10:475-81.
89. Asghar SJ, Tanay VA, Baker GB, et al. Relationship of plasma amphetamine levels to physiological, subjective, cognitive and biochemical measures in healthy volunteers. *Hum Psychopharmacol* 2003;18:291-9.
90. Brauer LH, Ambre J, De Wit H. Acute tolerance to subjective but not cardiovascular effects of d-amphetamine in normal, healthy men. *J Clin Psychopharmacol* 1996;16:72-6.
91. Angrist B, Corwin J, Bartlik B, et al. Early pharmacokinetics and clinical effects of oral D-amphetamine in normal subjects. *Biol Psychiatry* 1987;22:1357-68.
92. Silber BY, Croft RJ, Papafotiou K, et al. The acute effects of D-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology (Berl)* 2006;187:154-69.
93. Philips SR, Robson AM, Boulton AA. Unstimulated and amphetamine-stimulated release of endogenous noradrenaline and dopamine from rat brain in vivo. *J Neurochem* 1982;38:1106-10.
94. Pum M, Carey RJ, Huston JP, et al. Dissociating effects of cocaine and D-amphetamine on dopamine and serotonin in the perirhinal, entorhinal, and prefrontal cortex of freely moving rats. *Psychopharmacology (Berl)* 2007;193:375-90.
95. Kedzior KK, Badcock JC, Martin-Iverson MT. Validity and consistency of self-reports regarding substance use in general research volunteers, including regular cannabis users and schizophrenia patients. *Subst Use Misuse* 2006;41:743-50.