(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
07 November 2024 (07.11.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/227948 A1

(51) International Patent Classification:
A61B 5/16 (2006.01)

(21) International Application Number:
PCT/EP2024/062352

(22) International Filing Date:
03 May 2024 (03.05.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2306529.5 03 May 2023 (03.05.2023) GB

(71) Applicant: **UNIVERSITY OF BRISTOL** [GB/GB]; Senate House, Tyndall Avenue, Bristol Bristol BS8 1TH (GB).

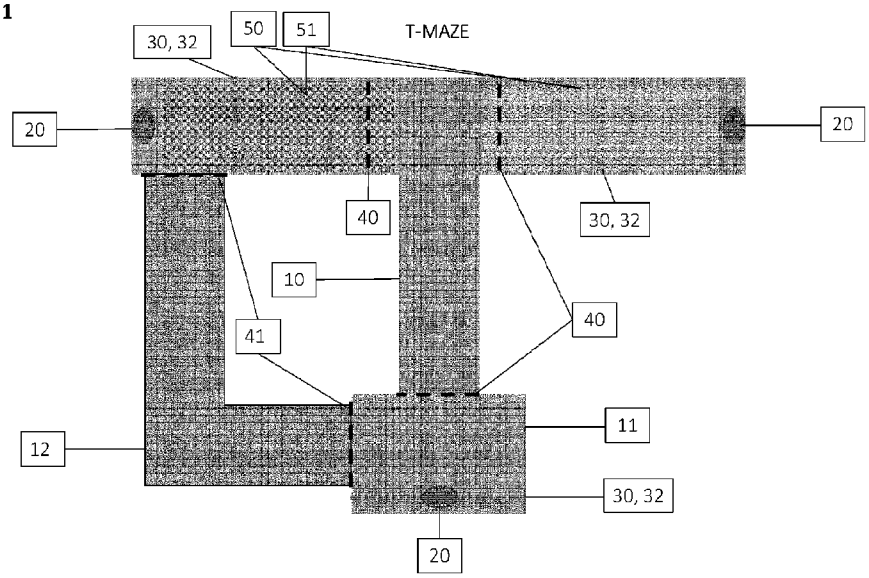
(72) Inventor: **ROBINSON, Emma**; c/o University of Bristol, Senate House, Tyndall Avenue, Bristol Bristol BS8 1TH (GB).

(74) Agent: **MEWBURN ELLIS LLP**; Aurora Building, Counterslip, Bristol BS1 6BX (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) **Title:** TESTING APPARATUS AND METHODS OF USE THEREOF

Figure 1



(57) **Abstract:** Apparatus for assessing the cognitive and/or emotional behaviour of a subject, comprising automated presenters configured to present complex sensory cues to a subject; and one or more actuatable reward dispensers configured to present rewards to the subject; wherein each complex sensory cue comprises (a) a substrate configured as to be distinguished by the subject in the somatosensory domain and optionally (b) a visual stimulus, an olfactory stimulus, and an auditory stimulus, or a combination thereof. Methods of assessing the cognitive and/or emotional behaviour of a subject; Methods of identifying a test compound and/or a risk gene that modifies the cognitive and/or emotional behaviour of a subject; and Methods of assembling apparatus disclosed herein are further provided.

WO 2024/227948 A1

[Continued on next page]

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

TESTING APPARATUS AND METHODS OF USE THEREOF

This application claims priority from GB 2306529.5 filed 03 May 2023, the contents and elements of which are herein incorporated by reference for all purposes.

Field of the Invention

The invention relates to apparatus for testing the behaviour of subjects, and methods of use thereof. Particularly, though not exclusively, the invention relates to apparatus for testing the behaviour of non-human subjects, such as laboratory animals.

Background

Automated behavioural testing is essential for the generation of reliable and reproducible data in non-human species. However, conventional behavioural testing apparatus relies on the use of cues in sensory domains which are not the predominant sense guiding complex cognitive behaviours in most non-human species. Conventional automated apparatus used in the testing of non-human subjects such as laboratory animals relies on stimuli provided in the spatial, visual and/or auditory domains. This is not ethologically relevant, thus fails to engage with the natural cognitive processes for the most common laboratory species, mice and rats.

Building from the era of Pavlov and Skinner, apparatus were developed to present animals with simple (single-domain) visual or spatial cues within a computer-controlled environment. In most studies, laboratory animals are trained to learn to perform a behavioural response (e.g., a nose poke in an aperture or a lever press response) in order to obtain a reward or to avoid an aversive outcome following stimulation with a sensory cue. Once this basic instrumental response has been achieved, the animal's behaviour can be shaped further using a wide variety of protocols which purport to measure different domains of cognition and executive function (such as attention, decision-making, cognitive flexibility, and working memory).

About 20 years ago, a technology was developed that utilises visual cues presented on a touch-sensitive screen. Test subjects (laboratory animals) are trained to make a touch response at the location of a visual cue, in order to obtain a reward. This development in the design of behavioural testing apparatus offers the advantage of providing visual stimuli that are independent of a specific spatial location however, vision is the sensory domain rodents use to avoid predation and is not their natural domain for cognition.

Both traditional operant conditioning chambers (Skinner boxes) and the touchscreen apparatus have a major disadvantage which reflects this poor alignment with natural behaviours. They require significant subject training (for example, to identify the appropriate cues, and to learn to perform a behaviour response in order to obtain a reward) before any behavioural testing can take place. This training commonly takes weeks or months to achieve and is heavily dependent on graduated training methods that are known to induce procedural learning. Although there may be elements of cognition involved in responding to conventional (e.g. touchscreen visual) cues, the ability of researchers to identify these in test subjects is heavily confounded by the influence of procedural learning.

In addition, conventional methods of behavioural testing are dependent upon maintaining subjects in a high motivational state, to ensure that the test subject will learn by performing a large number of responses within the session and hence develop the instrumental response (i.e., experimental replicates). This high motivational state may further confound the data generated and are associated with poorer welfare for the animals.

An alternative approach for the behavioural testing of rodents involves natural foraging behaviours often referred to as 'bowl-digging tasks', which more closely reflect ethologically relevant behaviours. Bowl-digging tasks require subjects to explore different digging substrates to find food reward which then lead to a cue-reward association. The methods take advantage of the ability to present non-spatial complex cues to the subject and is associated with much more rapid learning rates and more dynamic cognition. Using digging substrates as a cue, an animal can learn the basic response of digging for reward within a few sessions and can then learn a simple discrimination within a single session and less than 20 trials. However, conventional bowl-digging tasks are run manually by the experimental operator and are highly dependent upon the skills of the animal handler and are easily confounded by animal-handler interactions. This means that conventional bowl-digging assays are associated with poor reproducibility, and the time required to run a successful assay is prohibitive. Consequently, the use of bowl-digging assays is limited to specialist research groups. Moreover, bowl-digging assays are not compatible with the needs of the pharmaceutical industry. US2012095363A1 describes an automated system for presenting a compound tactile stimulus to a test subject.

The present invention has been devised in light of the above considerations.

Summary of the Invention

The invention provides apparatus for testing the cognitive and/or emotional behaviour of subjects, and methods of use thereof. The invention facilitates assessing the cognitive behaviour of a subject that have a greater translational potential, and that are more ethologically relevant for laboratory animals (particularly laboratory rodents), than conventional behavioural testing assays.

For example, because the invention enables the delivery of the reward to the subject at the same spatial locus as a complex sensory cue, the invention reduces the influence of spatial and procedural learning. Accordingly, the invention improves learning rates, accuracy and reliability of experimental data, and replicates bowl-digging tasks whist enabling better translational potential. Whilst US2012095363A1 describes an automated system for presenting a compound tactile stimulus to a test subject, the devices shown do not present a complex sensory cue at the same spatial locus at which a reward is delivered to the subject.

Furthermore, because the invention utilises automated systems to present complex sensory cues to the test subject, the interaction of the test subject with the experimental operator is reduced. This further improves accuracy and reliability of the experimental data and improves its reproducibility.

In this context, "*spatially co-located*" means that the complex sensory cue and the actuatable reward dispenser are co-located such that the interaction of the subject with the cue and the reward is not influenced by spatial or procedural learning.

As described herein, the subject may be a laboratory rodent. The term "*arranged as to be in simultaneous reach of the subject*" means that in use, the subject can physically contact the complex sensory cue and access the reward without moving between different locations within the apparatus. "*Reach*" of the subject in this context would be apparent to a person skilled in the art. For example, at a test locus, the complex sensory cue and the actuatable reward dispenser may be spatially separated by less than 15 cm; less than 10 cm; less than 5 cm or less than 1 cm. That is, the complex sensory cue and the actuatable reward dispenser may be spatially separated by less than 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, 6 cm, 7 cm, 8 cm, 9 cm, 10 cm, 11 cm, 12 cm, 13 cm, 14 cm or 15 cm.

Furthermore, by presenting the subject with complex sensory cues comprising a substrate configured as to be distinguished in the somatosensory domain, the invention provides testing assays that mimic the natural foraging behaviours of laboratory animals, particularly laboratory rodents. This reduces the training time needed to teach subjects to perform a task to obtain a reward and reduces the potential for procedural learning to drive the behaviours.

In this context, the term "*configured as to be distinguished in the somatosensory domain*" means that one substrate is configured so as to be differentiated from another substrate using touch alone (i.e., and not sight/sound/smell etc.).

In this context, the term "*substrate*" refers to one element of a complex sensory cue. The substrate is configured as to be distinguished by the subject in the somatosensory domain. The complex sensory cue may further visual stimuli, olfactory stimuli, auditory stimuli, or a combination thereof, thereby stimulating the subject in two or more sensory domains.

A first aspect of the invention provides apparatus for assessing the cognitive behaviour of a subject, comprising: a first test locus, comprising an automated presenter, configured as to present a first complex sensory cue to the subject; a second test locus, comprising an automated presenter, configured as to present a second complex sensory cue to the subject; in which the apparatus is configured as to permit movement of the subject between the test loci; and in which each complex sensory cue comprises a substrate configured as to be distinguished, by the subject, in the somatosensory domain. I.e., substrates that are configured as to be distinguished by the subject by touch alone. For example, textured substrates, substrates having tactile markings, or substrates having different material forms.

In some embodiments, the complex sensory cues may further comprise visual stimuli, olfactory stimuli, auditory stimuli, or a combination thereof, thereby providing stimuli the subject in two or more sensory domains.

In some embodiments, a substrate configured as to be distinguished by the subject in the somatosensory domain may comprise: one or more protrusions, extending at least 1 mm away from the surface of the substrate; and/or one or more recesses of at least 1 mm in the surface of the substrate. In some embodiments, one substrate configured as to be distinguished by the subject in the somatosensory domain may be substantially smooth. In some embodiments, the substrate configured as to be distinguished by the subject in the somatosensory domain may have an uneven surface. Suitable substates may comprise tactile markings. Suitable substrates may be textured. The substrate may be 3D-printed.

The substrate may be made of any material, such as plastic (e.g., a polymer) or metal. Suitable substrates may have a particular material form that is distinguishable in the somatosensory domain. For example, the substrate may be rough, hard, soft, or squashable. The substrate may be reusable or disposable. In some embodiments, the substrate may comprise openings or apertures, optionally configured as to enable the co-localised delivery of a visual stimulus, an olfactory stimulus, an auditory stimulus, or a combination thereof.

In some embodiments, the apparatus may further comprise a visual display unit, a loudspeaker (e.g. a tone generator), and/or a light source (e.g., a light emitting diode (LED)). In some embodiments, the automated presenter may comprise a visual display unit, a loudspeaker (e.g. a tone generator), and/or a light source (e.g., a light emitting diode (LED)). That is, the automated presenter may be configured to stimulate the subject in the somatosensory domain (via the presentation of a substrate as disclosed herein), alongside the provision of an additional visual stimulus, olfactory stimulus, auditory stimulus, or a combination thereof.

In some embodiments, each complex sensory cue and the actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject. The actuatable reward dispenser(s) may comprise a food dispenser or a drink dispenser. For example, the actuatable reward dispenser may be an openable window or an openable aperture through which the subject can access a reward, such as food or drink. The spatial co-location of the complex sensory cue and the actuatable reward dispenser is advantageous as to reduce the influence of spatial and procedural learning.

Apparatus of the invention may comprise more than two test loci, each test locus comprising an automated presenter, configured as to present a first complex sensory cue to the subject and an actuatable reward dispenser, configured as to present a reward to the subject in which each complex sensory cue comprises a substrate configured as to be distinguished, by the subject, in the somatosensory domain. For example, apparatus of the invention may comprise three (3), four (4), five (5), six (6), seven (7), eight (8), nine (9) or ten (10) test loci.

The automated presenters may be configured as to: select a first substrate configured as to be distinguished by the subject in the somatosensory domain from a first pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present that substrate to the subject at the first test locus; and select a second substrate configured as to be distinguished by the subject in the somatosensory domain from a second pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present that substrate to the subject at the second test locus; or select two different substrates configured as to be distinguished by the subject in the somatosensory domain from a single group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present one substrate to the subject at the first test locus and the other substrate to the subject at the second test locus. The automated presenters may be configured as to select the substrates configured as to be distinguished by the subject in the somatosensory domain from the pre-determined group(s) of substrates at random. The automated presenters may be configured as to select the substrates configured as to be distinguished by the subject in the somatosensory domain

from the pre-determined group(s) of substrates following a pre-determined sequence, such as a user-determined sequence.

In some embodiments, the automated presenter comprises a device capable of shuttling substrates along a rail. In some embodiments, the automated presenter comprises a device capable of selecting/presenting substrates on a wheel. In some embodiments, the automated presenter comprises a device capable of selecting/presenting substrates on a belt.

In some embodiments, the automated presenter is computer operated. The automated presenter may be operably connected to a computer, in which a computer software facilitates selection of the substrates from the pre-determined group(s) of substrates as described above. Accordingly, the methods of the second or third aspects of the invention may be computer-implemented. The use of automated presenters is advantageous in enabling the non-spatial presentation of complex sensory cues over multiple trials.

The apparatus may further comprise a start locus. The start locus may comprise a second actuatable reward dispenser, configured as to dispense a reward to the subject. The actuatable reward dispenser(s) may comprise a food dispenser or a drink dispenser.

The apparatus may further comprise one or more detectors, configured as to detect the location of the subject and/or any interaction of the subject with the first and/or second complex sensory cues. The one or more detectors may comprise a motion detector, such as an infrared motion sensor; and/or a force detector. Detecting interaction of the subject with the first complex sensory cue may comprise detecting movement of the subject towards and/or about the first test locus. Detecting interaction of the subject with the second complex sensory cue may comprise detecting movement of the subject towards and/or about the second test locus. Detecting interaction of the subject with a complex sensory cue may comprise detecting physical contact between the subject and the substrate configured as to be distinguished by the subject in the somatosensory domain. That is, detecting interaction of the subject with the first complex sensory cue may comprise detecting physical contact between the subject and the substrate at the first test locus. Detecting interaction of the subject with the second complex sensory cue may comprise detecting physical contact between the subject and the substrate at the second test locus. The apparatus may comprise a moveable response element with which the subject may interact, such as an actuatable button, lever, or movable bar, to facilitate detection of physical contact between the subject and the substrate. Detecting interaction of the subject with the first and/or second sensory cues may comprise detecting the presence of subject at the first and/or second test loci. Detecting interaction of the subject with the first and/or second sensory cues may occur by way of detecting force applied by the subject at sensors positioned about the first and/or second test loci. The actuatable reward dispenser(s) may be operably linked to the one or more of the detector(s).

In some embodiments, the apparatus may comprise a T-maze; in which the test loci are located at opposing arms of the T-maze. For example, the first and/or second complex sensory cues may be presented to the subject at the ''left'' or ''right'' arms of the maze.

In other embodiments, the apparatus may comprise a conventional skinner box or operant conditioning chamber having an internal surface in which the internal surface comprises the test loci, such

that the automated presenters and the actuatable reward dispenser are co-located and spatially arranged so as to be in simultaneous reach of the subject.

The apparatus may further comprise a 'return arm', connecting the test loci to a start locus. The apparatus may further comprise one or more barriers or doors restricting the subject's access to or between the test loci, or as relevant, the start locus. Suitable doors or barriers include retractable 'portcullis'-type or Guillotine doors, and one-way flaps. In some embodiments, the start locus comprises a start box, configured as to house the subject for a period of time prior to initiation of a behavioural testing assay.

In some embodiments, the apparatus may comprise a conventional skinner box or operant conditioning chamber apparatus, comprising one or more test loci positioned side-by-side on an internal surface. The first and/or second complex sensory cues may be presented to the subject via ''left'' or ''right'' openable windows or apertures positioned side-by-side on an internal surface of the chamber.

At each test locus, complex sensory cues are spatially co-located with the actuatable reward dispenser, so as to avoid or reduce the influence of spatial learning. Put differently, the automated presenters and the actuatable reward dispensers at each test locus are spatially co-located and arranged so as to be in simultaneous reach of the subject. For example, at a test locus, the complex sensory cue and the actuatable reward dispenser may be spatially separated by less than 15 cm; less than 10 cm; less than 5 cm or less than 1 cm. That is, the complex sensory cue and the actuatable reward dispenser may be spatially separated by less than 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, 6 cm, 7 cm, 8 cm, 9 cm, 10 cm, 11 cm, 12 cm, 13 cm, 14 cm or less than 15 cm.

In contrast, the test loci in embodiments of the invention are spatially separated from one-another. This is advantageous to allow two or more complex sensory cues to be presented to the subject simultaneously. Accordingly, apparatus of the invention are configured as to permit movement of the subject between the different test loci. For example, each test locus may be spatially separated by more than 15 cm; more than 10 cm; more than 5 cm or more than 1 cm. That is, the test loci spatially separated by more than 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, 6 cm, 7 cm, 8 cm, 9 cm, 10 cm, 11 cm, 12 cm, 13 cm, 14 cm or more than 15 cm.

The first and second complex sensory cues may be presented to the subject in pseudorandom order. For example, in embodiments of the invention in which the apparatus is a T-maze-type apparatus, the first and/or second complex sensory cues may be presented to the subject in pseudorandom order at the ''left'' or ''right'' arms of the maze. In embodiments in which the apparatus is an operant conditioning chamber, the first and/or second complex sensory cues may be presented to the subject in pseudorandom order via ''left'' or ''right'' openable windows or apertures.

The subject may be a non-human subject, such as a laboratory animal, for example, a laboratory rodent (e.g. a mouse, rat or guinea pig) or leporid (e.g., a rabbit), a cat, dog, sheep or pig, or a non-human primate (e.g. rhesus macaques or cynomolgus macaques).

In embodiments of the first aspect of the invention, the apparatus is an operant conditioning chamber apparatus for assessing the cognitive and/or emotional behaviour of a subject comprising: a first test locus comprising: a first automated presenter, configured as to present a first complex sensory cue to the

subject; a first actuatable reward dispenser, configured as to dispense a reward to the subject; and a first detector, configured as to detect interaction of the subject with the first complex sensory cue, wherein the first detector is operably linked to the first actuatable reward dispenser; a second test locus comprising: a second automated presenter, configured as to present a second complex sensory cue to the subject; a second actuatable reward dispenser, configured as to dispense a reward to the subject; and a second detector, configured as to detect interaction of the subject with the second complex sensory cue; wherein second detector is operably linked to the second actuatable reward dispenser; wherein at the first test locus, the first complex sensory cue and the first actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject; wherein at the second test locus, the second complex sensory cue and the second actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject; and wherein each complex sensory cue comprises a substrate configured as to be distinguished by the subject in the somatosensory domain; and optionally a visual stimulus, an olfactory stimulus, and an auditory stimulus, or a combination thereof.

In some embodiments, automated presenters are configured as to: (i) select the first substrate from a first pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain from a first pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present the substrate to the subject at the first test locus; and (ii) select the second substrate from a second pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present the substrate to the subject at the second test locus; or (iii) select the first and the second substrates configured as to be distinguished by the subject in the somatosensory domain from a single group of substrates configured as to be distinguished by the subject in the somatosensory domain, and to present the first substrate to the subject at the first test locus and the second substrate to the subject at the second test locus.

In some embodiments, the automated presenters are configured as to select the first and second substrates from the pre-determined group(s) of substrates at random.

In some embodiments, the automated presenters are configured as to select the first and second substrates from the pre-determined group(s) of substrates following a pre-determined sequence, optionally a user-determined sequence.

In some embodiments, the automated presenters comprise a belt, the belt comprising a pre-determined group of substrates, each substrate configured to be distinguished by the subject in the somatosensory domain.

In some embodiments, the actuatable reward dispensers comprise food dispensers or drink dispensers.

In some embodiments, the actuatable reward dispensers comprise openable windows or openable apertures through which the subject may access a reward.

In some embodiments, the detectors are configured as to detect the interaction of the subject with the first and/or second complex sensory cues; for example, the detectors may be configured as to detect physical contact between the subject and the first and/or second substrates. In some embodiments, the one or more detectors comprise movable elements; optionally a plurality of moveable bars, or a moveable ladder.

In some embodiments, the substrates: (i) comprise one or more protrusions, extending at least 1 mm away from the surface of the substrate; (ii) comprise one or more recesses of at least 1 mm in the surface of the substrate; (iii) comprise a surface that is substantially smooth; (iv) comprise tactile markings; and/or (v) are of a material form configured as to be distinguished by the subject in the somatosensory domain.

In some embodiments, the subject is non-human; optionally wherein the subject is a laboratory animal, such as a laboratory rodent.

A second aspect of the invention provides a method for assessing the cognitive and/or emotional behaviour of a subject, using the apparatus of the first aspect of the invention; the method comprising: presenting the subject with a first complex sensory cue at a first test locus by way of an automated presenter, and a second complex sensory cue at a second test locus by way of an automated presenter; detecting the interaction of the subject with the first and/or second complex sensory cues; and providing the subject with a reward following their interaction with the first complex sensory cue; but not following their interaction with second complex sensory cue; in which the reward is accessible to the subject at the first test locus.

A third aspect of the invention provides a method for identifying a test compound or risk gene that modifies the cognitive and/or emotional behaviour of a subject, using the apparatus of the first aspect of the invention; the method comprising: administering the subject a test compound that modifies the cognitive and/or emotional behaviour of the subject; presenting the subject with a first complex sensory cue at a first test locus by way of an automated presenter, and a second complex sensory cue at a second test locus by way of an automated presenter; detecting the interaction of the subject with the first and/or second complex sensory cues; and providing the subject with a reward following their interaction with the first complex sensory cue; but not following their interaction with second complex sensory cue; in which the reward is accessible to the subject at the first test locus; in which the test compound is identified as modifying the cognitive and/or emotional behaviour of the subject, if: the duration of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or the frequency of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or in which the risk gene is identified as modifying the cognitive and/or emotional behaviour of the subject, if: the duration of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or the frequency of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control.

In this context, the term "*risk gene*" should be understood as meaning a gene that regulates or is suspected of regulating, directly or indirectly, the cognitive and/or emotional behaviour of a subject. For example, the presence of a risk gene in a subject may make that subject more or less likely to display modified cognitive or emotional behaviour.

In some embodiments, the control may comprise: a reference value; a subject administered a placebo agent, and not a test compound capable of modifying the cognitive and/or emotional behaviour of the subject; a subject administered a test compound that is known not to modify the cognitive and/or emotional behaviour of said subject; a subject administered a pharmacologically active agent that is known to modify the cognitive and/or emotional behaviour of said subject; and/or a subject not having manipulated expression of a risk gene. Test compounds may include any compound having a mode of action relevant to modulating the cognitive and/or emotional behaviour of a subject, or any compound having adverse events related to changes in cognitive and/or emotional behaviour. Examples of drug classes which may be tested including novel antidepressants, cognitive enhancers, drugs affecting motivation and impulse control. In some embodiments, the subject may be engineered or genetically modified. For example, the subject may comprise a modification, genetic or otherwise, that modifies a target polynucleotide sequence in a cell, or that modifies the expression of a target polypeptide in a cell. The subject may comprise a genetic mutation in a disease gene, or a “knock out” gene mutation. Methods of genetic modification may further comprise repairing or editing target polynucleotide by inserting an exogenous template polynucleotide, wherein the repair or editing results in a mutation comprising an insertion, deletion, or substitution of one or more nucleotides of the target polynucleotide. For example, a modified subject may be produced by manipulating a gene in a whole animal, specific neural pathway and/or specific cell type that is associated with the central nervous system and linked to cognitive and/or emotional behaviour.

A fourth aspect of the invention provides a method comprising: joining the first substrate configured as to be distinguished by the subject in the somatosensory domain to an automated presenter, configured as to present a complex sensory cue to the subject at a first test locus; and/or joining the second substrate configured as to be distinguished by the subject in the somatosensory domain to an automated presenter, configured as to present a complex sensory cue to the subject at a second test locus; in which the test apparatus further comprises: an actuatable reward dispenser, configured as to dispense a reward to the subject; in which the apparatus is configured as to permit movement of the subject between the test loci; in which the substrates are configured as to be distinguished by the subject in the somatosensory domain.

A fifth aspect of the invention provides use of an apparatus according to the first aspect of the invention in a method according to the second or third aspects of the invention.

A sixth aspect of the invention provides a kit of parts, comprising: the apparatus for assessing the cognitive behaviour of a subject of the first aspect of the invention; and one or more substrates configured as to be distinguished by the subject by the subject in the somatosensory domain.

The invention also includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

Summary of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures:

Figure 1 is a schematic diagram of a T-maze-type testing apparatus.

Figure 2 shows a perspective view of an exemplary first automated presenter.

Figure 3 shows a schematic diagram a second automated presenter.

Figure 4 is a schematic diagram of a T-maze-type apparatus that is suitable for use with laboratory rodents.

Figure 5 shows a perspective view of an exemplary T-maze-type apparatus. This apparatus was used to generate the proof-of-concept data illustrated in Figure 8 and 9

Figure 6 shows a perspective view of an exemplary T-maze-type apparatus with the automated presenter rail design of Figure 2.

Figure 7 shows a schematic diagram of an operant conditioning chamber- apparatus and provides a schematic diagram of a third automated presenter.

Figure 8 shows a first perspective view of an exemplary operant conditioning chamber apparatus. The automated presenter is a belt-type design.

Figure 9 shows a second perspective view of the apparatus of Figure 8.

Figure 10 (A) shows a detailed view of the belt-type automated presenter and the detector used in the apparatus of Figures 8 and 9. In panel **(B)**, elements of the automated presenter and the detector are removed to show the underlying workings of the system.

Figure 11 shows results from a pilot experiment carried out using the prototype shown in Fig 5. **(A)** Associative learning was measured in individual rats, confirming a fast rate of learning with all animals performing above chance (50%) within the first session. **(B)** An assay was performed to test data replication between apparatus of the invention and a conventional a bowl-digging task. A cohort of rats were subject to a reward learning assay using the protocol illustrated in **(C).** The location of the star symbol indicates the provision of a reward. The presence of two "*" symbols indicates the provision of "high reward". The ">" and "<" symbols indicate the preference of the subject for a particular somatosensory substrate. The data show a full replication of a reward-induced bias of similar magnitude and variability as the same task run in the manual bowl-digging task.

Figure 12 shows results from a pilot experiment carried out using the prototype shown in Fig 5. The study performed an affective bias induction protocol to establish if the affective bias assay, previously run in the manual bowl digging apparatus, could be replicated in the complex cue T-maze. Results from the learning phase of the task **(A)** and preference test **(B)** demonstrate the induction of either a positive or negative affective bias consistent with previous findings. The affective bias protocol is shown in panel **(C)**. The location of the star symbol indicates the provision of a reward. The ">" and "<" symbols indicate the preference of the subject for a particular somatosensory substrate.

Detailed Description of the Invention

Aspects and embodiments of the present invention will now be discussed with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Figure 1 shows a T-maze-type apparatus (10) as disclosed herein, comprising first ("Left") and second ("Right") test loci. In this example, the apparatus comprises a start locus (11). Actuatable reward dispensers (20) are positioned at each of the test loci and the start locus. Suitable actuatable reward dispensers include food dispensers and drink dispensers. The actuatable reward dispensers may be operably linked to one or more detectors (30), configured as to detect interaction of the subject with the first and/or second complex sensory cues. Detectors may also be positioned at the start locus (30), configured as to detect the presence of the test subject at the start locus. In this example, the detectors comprise infrared motion sensors (32). Other suitable detectors include alternative motion detectors, force sensors touch operated buttons, moveable elements and the like. In some embodiments, detecting interaction of the subject with a complex sensory cue may involve detecting movement of the subject towards and/or about a test locus. Detecting the interaction of the subject with the first complex sensory cue may involve detecting movement of the subject towards and/or about the first test locus. Detecting the interaction of the subject with the second complex sensory cue may involve detecting movement of the subject towards and/or about the second test locus.

As an alternative, or in addition, detecting the interaction of the subject with a complex sensory cue may involve detecting physical contact of the subject and a substrate configured as to be distinguished by the subject in the somatosensory domain. Detecting the interaction of the subject with the first complex sensory cue may involve detecting physical contact of the subject and the first substrate configured as to be distinguished by the subject in the somatosensory domain at the first test locus. Detecting the interaction of the subject with the second complex sensory cue may involve detecting physical contact of the subject and the second substrate configured as to be distinguished by the subject in the somatosensory domain at the second test locus.

Detecting the interaction of the subject with the first and/or second sensory cues may involve detecting the presence of subject at the first and/or second test loci. In some embodiments, detecting the interaction of the subject with the first and/or second sensory cues involves detecting force applied by the subject at sensors positioned about the test loci.

Apparatus of the invention may further comprise a 'return arm' (12) connecting the test loci to the start locus and configured so as to permit movement of the subject between the test loci and the start locus. Similarly, apparatus of the invention may further comprise one or more barriers or doors (40). In the example of Figure 1, three retractable 'portcullis' type doors are positioned so as to restrict the subject's access to the first and second test loci, and the start locus, and two one-way flaps (41) are positioned at each end of the return arm.

At the test loci, the subject is presented with a complex sensory cue (50) comprising a substrate configured as to be distinguished by the subject in the somatosensory domain (51), and additional stimuli in multiple sensory domains (e.g., visual olfactory, and/or auditory stimuli). In the example of Figure 1, the complex

sensory cues comprise textured flooring. Suitable alternatives include textured wall elements, textured ceiling elements and the like. A substrate configured as to be distinguished by the subject in the somatosensory domain may comprise one of more protrusions, extending at least 1 mm away from the surface of the substrate; and/or one or more recesses of at least 1 mm in the surface of the substrate. Alternatively, the substrate may be substantially smooth. Moreover, complex sensory cues may comprise stimuli in two or more sensory domains. For example, visual stimuli, olfactory stimuli, and/or auditory stimuli (in addition to the substrate configured as to be distinguished by the subject in the somatosensory domain and configured so as to be distinguishable by the subject in the somatosensory domain). Each complex sensory cue is presented to the subject by way of an automated presenter (not shown).

Figure 2 shows one example of a suitable automated presenter. Substrates configured as to be distinguished by the subject in the somatosensory domain (51) (here textured flooring elements) may be automatically shuttled along a rail guide (61) for presentation to the subject at the first and/or second test loci by automated presenters (60).

Figure 3 shows another example of a suitable automated presenter. Here, substrates configured as to be distinguished by the subject in the somatosensory domain (51) are selected from a rack-type automated presenter (60,62) for presentation to the subject at the first or second test loci, as complex sensory cues (50). At each test locus, actuatable reward dispenser(s) (20) are spatially co-located with the complex sensory cues and arranged as to be in simultaneous reach of the subject. Automated presenters (60) may be configured as to select the substrates (51) from the pre-determined group(s) of substrates at random, or following a pre-determined sequence, such as a user-determined sequence. The automated presenter (60) may be configured as to select a first substrate configured as to be distinguished by the subject in the somatosensory domain (51) from a first pre-determined group of substrates, and present that substrate to the subject at the first test locus; and to select a second substrate configured as to be distinguished by the subject in the somatosensory domain (51) from a second pre-determined group of substrates, and present that substrate to the subject at the second test locus; or to select two different substrates (51) from a single group of substrates, and to present one substrate to the subject at the first test locus and the other substrate to the subject at the second test locus.

In some embodiments, the subject is non-human. For example, the subject may be a laboratory animal, such as a laboratory rodent. Figure 4 shows a T-maze-type apparatus (10) having a start locus (11) that is of suitable size for use with laboratory rodents. The longest edge of the apparatus measures 36cm, meaning that the apparatus is convenient for use in a laboratory setting, where space is at a premium.

Figure 5 shows a perspective view of an exemplary T-maze-type apparatus (10), having a start locus (11) and in which the complex sensory cues (50) comprise a plurality of individual substrates configured as to be distinguished by the subject in the somatosensory domain (52). The substrates are presented to the subject at the first and second test loci by way of an automated presenter (not shown).

Figure 6 shows a perspective view of a second exemplary T-maze-type apparatus (10). The apparatus comprises a start locus (11), and two test loci ("right" and "left" arms of the T-maze). Actuatable reward dispensers (20) are positioned at each of the test loci and the start locus. In this example, food pellet dispensers (21) are spatially co-located with the complex sensory cues (50) at the test loci. The complex sensory cues each comprise a substrate configured as to be distinguished by the subject in the somatosensory domain (51). An additional actuatable reward dispenser is also provided at the start locus (20,21). In this example, the complex sensory cues comprise substrates configured as to be distinguished by the subject in the somatosensory domain (51) (textured flooring elements, not shown) that are presented to the subject by way of two automated presenters (60). The automated presenters shuttle the textured substrates along a rail guide (61) for presentation to the subject at the first and/or second test loci. That is, the automated presenters (60) are each configured as to select a first substrate configured as to be distinguished by the subject in the somatosensory domain (51) from a first pre-determined group of substrates, and present that substrate to the subject at the first test locus; and to select a second substrate configured as to be distinguished by the subject in the somatosensory domain (51) from a second pre-determined group of substrates, and present that substrate to the subject at the second test locus.

The actuatable reward dispensers may be operably linked to one or more detectors (30), configured as to detect interaction of the subject with the first and/or second complex sensory cues. In this example, the apparatus comprises two infrared sensors (32). One detector is configured as to detect the interaction of the subject with the first complex sensory cue (50) (at the first test locus) and the other detector is configured as to detect interaction of the subject with the second complex sensory cue (50) (at the second test locus). A third detector (30) is provided at the start locus. Three doors (40) of a Guillotine-type (41) are provided to enclose each of the test loci and the start locus.

Figure 7 illustrates an operant conditioning chamber apparatus (13) of the invention having an internal surface (14), comprising two loci. At two test loci ("left" and "right"), an automated presenter (60) act to present substrates configured as to be distinguished by the subject in the somatosensory domain (51) to the subject via a belt system (63). The substrates are presented as complex sensory cues (50) alongside stimuli in multiple sensory domains (e.g., visual olfactory, and/or auditory stimuli). As shown, actuatable reward dispensers (20) are spatially co-located with the complex sensory cues (50), such that the cues and the rewards are delivered in simultaneous reach of the subject.

Figure 8 shows an exemplary operant conditioning chamber apparatus (13) as disclosed herein, having an internal surface (14) that comprises two test loci ("left" and "right"). Each test locus comprises an openable window or aperture (70) through which an automated presenter (60) presents a complex sensory cue (50) to the subject. The cues comprise a substrate configured as to be distinguished by the subject in the somatosensory domain (51), and optionally additional visual/audible/olfactory stimuli. The automated presenter (60) selects and presents the substrates (51) to the subject by way of a belt system (63). At each test locus, a detector (30) in the form of a movable bar (33) is positioned behind the openable window/aperture (70) but in front of the substrate (51) such that the moveable bar may be used to detect interaction of the subject with the substrate (51). In use, as the subject reaches through the window (70)

to contact the substrate (51), the detector (30, 33) is moved, thereby registering interaction of the subject with the substrate (51). Actuatable reward dispensers (20) are positioned at each of the test loci. Each dispenser (20) is spatially co-located with the complex sensory cue (50) the respective complex sensory cue and is arranged as to be in simultaneous reach of the subject. In this example, food pellet dispensers (21) are positioned under the openable window/aperture (70). The actuatable reward dispensers (20, 21) are operably linked to the detector (30,33), such that interaction of the subject with the substrate (51) causes movement of the moveable bar (33), which in turn causes a reward to be dispensed.

Figure 9 shows part of the external arrangement of the operant conditioning chamber apparatus (13) of Figure 8, such that the automated presenter (60) can be seen in more detail. Substrates configured to be distinguished by the subject in the somatosensory domain (51) are presented to the subject via a belt (63). The belt-type presenter (60, 63) is computer operated (not shown). A detector (30) in the form of a moveable bar (33) is operably linked to an actuatable reward dispenser (20a), positioned directly underneath the automated presenter such that both are spatially co-located. On the “right” side of the operant conditioning chamber, the automated presenter (60) and detector (30) systems have been removed, thereby providing a clear view of the openable window/aperture (70) through which the subject may interact with the complex sensory cue. The window (70) is spatially co-located with an actuatable reward dispenser (20). In use, the actuatable reward dispenser (20) would be similarly co-located with the automated presenter (60).

Figure 10A shows an exemplary automated presenter (60) as disclosed herein. The automated presenter (60) comprises a belt (63) comprising a series of substrates configured to be distinguished by the subject in the somatosensory domain (51). In use, the automated presenter (60) drives the belt (63) to select a substrate (51) from a pre-determined group of substrates and presents that substrate to the subject at a test locus. The automated presenter is joined to a detector (30), the detector comprising moveable bars (33). In use, the detector (30, 33) acts to detect interaction (physical contact) of the subject with the substrate (51). In apparatus of the invention, the detector (30, 33) may be operably linked to an actuatable reward dispenser (not shown). As shown in Figure 8, apparatus of the invention may comprise two or more automated presenters (60) or detectors (30) as disclosed herein. Per Figure 10B, the belt (63) is driven on a pair of rollers (64), which may be computer operated (not shown). In this embodiment, the detector comprises a set of wheels (34) operably joined to the moveable bars (not shown). In use, movement of the moveable bars causes a corresponding movement in the detector wheels (34), thereby registering an interaction between the subject and the underlying substrate (51) e.g. using an external recording device such as a computer (not shown).

Experimental Data

Example study protocol:

Stage 1: Habituation – the subject is allowed to freely explore the apparatus with food reward dispensed randomly in each of the test loci.

Stage 2: Shuttle training – subjects are first held in a start box. One of the test loci is baited with a reward then the start box is opened. The subject is free to explore both test loci but when it returns to the

start box, a sensor detects its location, delivers a reward and the start box door is closed. This is repeated for multiple trials and over more than one session (e.g., across multiple days) until the subject has learnt to leave the start box, collect the reward from one of the test loci and return to the start box – classified as a single trial. Multiple trials may be completed with a single test session.

Stage 3: Discrimination training - subjects are first held in a start box. The test loci are set-up to the first of the complex sensory cue sequences where a different complex sensory cue is presented in each of the test loci. The start box is opened and the subject is free to explore both test loci, but when it enters one of the test loci, it triggers a sensor which results in one of two outcomes – if the 'correct' choice is made (e.g., the subject interacts with the 'correct' complex sensory cue), then a reward is delivered at the same location (e.g., in reach of the subject), and the door to the other 'incorrect' test locus location is closed. If the 'incorrect' choice is made (e.g., the subject interacts with the 'incorrect' complex sensory cue), then no reward is delivered, and the door to the other 'correct' test locus is closed. If the subject returns to the start box, it triggers a sensor, and the start box door is closed. A reward may or may not be dispensed in the start box. The complex sensory cue sequence then automatically moves to the next trial sequence, and a new trial starts with the start box door opening. Multiple trials may be completed within a single test session. Subjects continue through stages 2 and 3 until they meet the necessary test criteria (>80% accuracy). Subjects are considered fully trained once they achieve >80% accuracy in a discrimination session (stage 3).

Experiment 1: Assessment of associative learning and reward-induced bias

This experiment tested whether the prototype apparatus could be used to replicate the learning rate and reward-induced bias which is observed in a bowl digging task. We tested whether animals would a) learn the discrimination to an accuracy above chance (50%) in a single test session of 20 trials and b) if they develop a reward-induced bias following independent learning of the cue-reward associations and testing in a choice test.

Animals undergo independent associative learning sessions where they discriminate between rewarded and unrewarded cues to obtain a food reward. Each learning session consists of one pairs of cues where one is rewarded and the other unrewarded and the animal must learn by trial and error which cue predicts reward. In the version of the task illustrated in Figure 11, the animals learn a high reward vs no reward discrimination on one session and a low reward vs no reward discrimination on a second session. A session consists of presenting each cue in either the left or right location using a pseudorandom spatial presentation. In this example, each session consisted of 20 trials where the animal started from the start box and made a choice for the left or right location. If they were correct, they were rewarded and if they were incorrect, they were not rewarded. After each choice is made, the appropriate door closes off the unselected arm and then animal must return to the start box to initiate the next trial. Once animals return to the start location, the start box door closes, and the locations of the complex cues are re-set using the pseudorandom spatial order then the next trial starts with the start door opening. The learning sessions were repeated once for each pair of cues. To test if animals developed a reward-induced bias, a further session was run using a choice test to assess if the animals have learnt to use their past experiences to bias their choices towards the higher value reward-paired cue. In this session both the previously

rewarded cues are presented to the animal and their choices over 20 trials recorded. For this choice test, the cues are randomly reinforced at a rate of 1 in 3 to avoid new learning and drive the behaviour based on past experiences. As illustrated in Figure 11, animals show learning rates above chance for each of the discrimination learning sessions. A reward-induced bias is also observed when the animal makes more choices for the cue that predicts the high value reward. These data replicate the findings from the bowl digging set-up in the complex cue T-maze apparatus. The study was performed using laboratory rodents.

Experiment 2: Assessment of bias induction

The affective bias test is a novel behavioural task designed to recapitulate in animals the neuropsychological phenomenon of an affective state induced cognitive bias. These affective biases arise when the emotional state of the subject influence their cognition and influence learning and memory, decision-making and attention and offer an important translational model for psychiatry research. The affective bias task has been run in a bowl digging set-up and this experiment sought to replicate the findings in the T-maze. In this experiment (Figure 12), the animals learn a two independent cue-reward association during discrimination learning sessions. During each session the value of the reward earnt is the same, but the affective state of the animal is manipulated during the learning session. In this experiment, affective state was changed by treating the animal with a drug. One cue-reward association is learnt during the affective state manipulation (positive state induction using the antidepressant venlafaxine or negative induction using the anxiogenic and pro-depressant drug, FG7142) and the other in a neutral state (vehicle treatment). Animals show rapid learning similar to rates seen in the bowl digging task. The main outcome measure for this task is to test if an affective bias has been generated. This is tested by presenting both the previously rewarded cues in the same session in a choice test with random reinforcement to maintain responding but avoid new learning and drive the behaviour based on past experiences. In this experiment, the T-maze apparatus procedure replicated induction and quantification of either a positive or negative affective bias. The study was performed using laboratory rodents.

These experimental data were generated using a T maze-type apparatus of the invention. Nonetheless, the present inventors believe that the same advantages would be apparent if the studies were to be reproduced using an operant conditioning chamber apparatus of the invention. Without being bound to a particular theory, both the T maze-type apparatus and the operant conditioning chamber apparatus disclosed herein enable the delivery of a reward to the subject at the same spatial locus as a complex sensory cue, thereby reducing the influence of spatial and procedural learning.

The features disclosed in the foregoing description, or in the following claims, or in the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for obtaining the disclosed results, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

While the invention has been described in conjunction with the exemplary embodiments described above, many equivalent modifications and variations will be apparent to those skilled in the art when given this disclosure. Accordingly, the exemplary embodiments of the invention set forth above are considered to be illustrative and not limiting. Various changes to the described embodiments may be made without departing from the spirit and scope of the invention.

For the avoidance of any doubt, any theoretical explanations provided herein are provided for the purposes of improving the understanding of a reader. The inventors do not wish to be bound by any of these theoretical explanations.

Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise" and "include", and variations such as "comprises", "comprising", and "including" will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment. The term "about" in relation to a numerical value is optional and means for example +/- 10%.

References

A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. The entirety of these references is incorporated herein by reference, for all purposes.

Editorial/opinion articles

Stanford (2020) Some Reasons Why Preclinical Studies of Psychiatric Disorders Fail to Translate: What can Be Rescued from the Misunderstanding and Misuse of Animal 'Models'? Alternatives to animal models, Altern Lab Anim 48: 106–115.

Söderlund J, Lindskog M (2018) Relevance of rodent models of depression in clinical practice: can we overcome the obstacles in translational neuropsychiatry? Int J Neuropsychopharmacol 21: 668–676.

Cuthbert (2022) Research Domain Criteria (RDoC): Progress and Potential. Curr Dir Psychol Sci. 2022 31(2): 107–114.

Pratt et al., (2022) BAP editorial: Improving the validity and translation of preclinical research. J Psychopharm, 36, (7) https://doi.org/10.1177/0269881122110406

Touchscreen apparatus

Horner et al., (2013) (2013). The touchscreen operant platform for testing learning and memory in rats and mice. Nature Protocols, 8(10), 1961–1984.

Bowl digging tasks

Tait et al., (2014) Attentional set-shifting in rodents: a review of behavioural methods and pharmacological results. Curr Pharm Des 20(31):5046-59.

Heisler et al., (2015) The Attentional Set Shifting Task: A Measure of Cognitive Flexibility in Mice. J Vis Exp. 2015; (96): 51944.

Stuart et al., (2013) A translational rodent assay of affective biases in depression and antidepressant therapy. Neuropsychopharmacology 38 (9), 1625-1635

Robinson (2018) Translational new approaches for investigating mood disorders in rodents and what they may reveal about the underlying neurobiology of major depressive disorder. Philosophical Transactions of the Royal Society B: Biological Sciences, 373(1742), 20170036.

Claims:

1. An apparatus for assessing the cognitive and/or emotional behaviour of a subject, comprising

(i) a first test locus, comprising an automated presenter, configured as to present a first complex sensory cue to the subject;

(ii) a second test locus, comprising an automated presenter, configured as to present a second complex sensory cue to the subject; and

one or more actuatable reward dispensers, configured as to present a reward to the subject;

wherein the apparatus is configured as to permit movement of the subject between the first test and second test loci; and

wherein each complex sensory cue comprises (a) a substrate configured as to be distinguished by the subject in the somatosensory domain; and optionally (b) a visual stimulus, an olfactory stimulus, and an auditory stimulus, or a combination thereof.

2. The apparatus of claim 1, wherein at the first test locus, the first complex sensory cue and a first actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject; and wherein at the second test locus, the second complex sensory cue and a second actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject.

3. The apparatus of any one of claims 1 or 2, wherein the apparatus comprises a T-maze.

4. The apparatus of any one of claims 1 or 2, wherein the apparatus comprises an operant conditioning chamber.

5. The apparatus of any one of claims 1 to 4, wherein the automated presenters are configured as to:

(i) select a first substrate configured as to be distinguished by the subject in the somatosensory domain from a first pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present that substrate to the subject at the first test locus; and

(ii) select a second substrate configured as to be distinguished by the subject in the somatosensory domain from a second pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present that substrate to the subject at the second test locus; or

(iii) select two different substrates configured as to be distinguished by the subject in the somatosensory domain from a single group of substrates configured as to be distinguished by the subject in the somatosensory domain, and to present one substrate to the subject at the first test locus and the other substrate to the subject at the second test locus.

6. The apparatus of claim 5, wherein the automated presenters are configured as to select the substrates from the pre-determined group(s) of substrates at random.

7. The apparatus of claim 5, wherein the automated presenters are configured as to select the substrates from the pre-determined group(s) of substrates following a pre-determined sequence, optionally a user-determined sequence.

8. The apparatus of any one of claims 1 to 7, further comprising a start locus, optionally wherein the start locus comprises an actuatable reward dispenser, configured as to dispense a reward to the subject.

9. The apparatus of any one of claims 1 to 8, wherein the actuatable reward dispenser comprises a food dispenser or a drink dispenser.

10. The apparatus of any one of claims 1 to 9, wherein the actuatable reward dispenser comprises an openable window or an openable aperture through which the subject may access a reward.

11. The apparatus of any one of claims 1 to 10, further comprising one or more detectors, configured as to detect the interaction of the subject with the first and/or second complex sensory cues.

12. The apparatus of claim 11, wherein the one or more detectors comprise a movable element, optionally a moveable bar.

13. The apparatus of claim 11 or claim 12, wherein the one or more detectors comprise a motion detector, optionally an infrared motion sensor; and/or a force detector, optionally a touch-operated button.

14. The apparatus of any one of claims 11 to 13, wherein detecting interaction of the subject with the first complex sensory cue comprises detecting movement of the subject towards and/or about the first test locus; and/or wherein detecting the interaction of the subject with the second complex sensory cue comprises detecting movement of the subject towards and/or about the second test locus.

15 The apparatus of any one of claims 11 to 14, wherein detecting the interaction of the subject with the first complex sensory cue comprises detecting physical contact of the subject and the substrate configured as to be distinguished by the subject in the somatosensory domain at the first test locus; and/or wherein detecting the interaction of the subject with the second complex sensory cue comprises detecting physical contact of the subject and the substrate configured as to be distinguished by the subject in the somatosensory domain at the second test locus.

16. The apparatus of any one of claims 11 to 15, wherein detecting the interaction of the subject with the first and/or second complex sensory cues comprises detecting the presence of subject at the first test and/or second test loci.

17. The apparatus of any one of claims 11 to 16, wherein detecting the interaction of the subject with the first and/or second complex sensory cues comprises detecting force applied by the subject at sensors positioned about the first test and/or second test loci.

18. The apparatus of any one of claims 11 to 17, wherein the actuatable reward dispenser is operably linked to the one or more detectors.

19. The apparatus of any one of claims 1 to 18, wherein the substrate configured as to be distinguished by the subject in the somatosensory domain:

(i) comprises one or more protrusions, extending at least 1 mm away from the surface of the substrate; and/or

(ii) comprises one or more recesses of at least 1 mm in the surface of the substrate; and/or

(iii) comprises a surface that is substantially smooth; and/or

(iv) comprises tactile markings; and/or

(v) is of a material form configured as to be distinguished by the subject in the somatosensory domain.

20 The apparatus of any one of claims 1 to 19, wherein the subject is non-human; optionally wherein the subject is a laboratory animal, such as a laboratory rodent.

21. An operant conditioning chamber apparatus for assessing the cognitive and/or emotional behaviour of a subject comprising:

(i) a first test locus comprising:

a. a first automated presenter, configured as to present a first complex sensory cue to the subject;

b. a first actuatable reward dispenser, configured as to dispense a reward to the subject; and

c. a first detector, configured as to detect interaction of the subject with the first complex sensory cue,

wherein the first detector is operably linked to the first actuatable reward dispenser;

(ii) a second test locus comprising:

a. a second automated presenter, configured as to present a second complex sensory cue to the subject;

b. a second actuatable reward dispenser, configured as to dispense a reward to the subject; and

c. a second detector, configured as to detect interaction of the subject with the second complex sensory cue;

wherein second detector is operably linked to the second actuatable reward dispenser;

wherein at the first test locus, the first complex sensory cue and the first actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject;

wherein at the second test locus, the second complex sensory cue and the second actuatable reward dispenser are spatially co-located and arranged as to be in simultaneous reach of the subject; and

wherein each complex sensory cue comprises (a) a substrate configured as to be distinguished by the subject in the somatosensory domain; and optionally (b) a visual stimulus, an olfactory stimulus, and an auditory stimulus, or a combination thereof.

22. The apparatus of claim 21, wherein the automated presenters are configured as to:

(i) select the first substrate configured as to be distinguished by the subject in the somatosensory domain from a first pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present the substrate to the subject at the first test locus; and

(ii) select the second substrate configured as to be distinguished by the subject in the somatosensory domain from a second pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain, and present the substrate to the subject at the second test locus; or

(iii) select the first and the second substrates configured as to be distinguished by the subject in the somatosensory domain from a single group of substrates configured as to be distinguished by the subject in the somatosensory domain, and to present the first substrate to the subject at the first test locus and the second substrate to the subject at the second test locus.

23. The apparatus of claim 22, wherein the automated presenters are configured as to select the first and second substrates from the pre-determined group(s) of substrates at random.

24. The apparatus of claim 22, wherein the automated presenters are configured as to select the first and second substrates from the pre-determined group(s) of substrates following a pre-determined sequence, optionally a user-determined sequence.

25. The apparatus of any one of claims 21 to 24, wherein the automated presenters comprise a belt, the belt comprising a pre-determined group of substrates configured as to be distinguished by the subject in the somatosensory domain.

26. The apparatus of any one of claims 21 to 25, wherein the actuatable reward dispensers comprise food dispensers or drink dispensers.

27. The apparatus of any one of claims 21 to 26, wherein the actuatable reward dispensers comprise openable windows or openable apertures through which the subject may access a reward.

28. The apparatus of any one of claims 21 to 27, wherein the detectors are configured as to detect the interaction of the subject with the first and/or second complex sensory cues; optionally wherein the detectors are configured as to detect physical contact between the subject and the first and/or second substrates.

29. The apparatus of claim 28, wherein the one or more detectors comprise movable elements optionally wherein the moveable elements are a plurality of moveable bars, or a moveable ladder.

30. The apparatus of any one of claims 21 to 29, wherein the substrates:

(i) comprise one or more protrusions, extending at least 1 mm away from the surface of the substrate; and/or

(ii) comprise one or more recesses of at least 1 mm in the surface of the substrate; and/or

(iii) comprise a surface that is substantially smooth; and/or

(iv) comprise tactile markings; and/or

(v) are of a material form configured as to be distinguished by the subject in the somatosensory domain.

31 The apparatus of any one of claims 21 to 30, wherein the subject is non-human; optionally wherein the subject is a laboratory animal, such as a laboratory rodent.

32. A method for assessing the cognitive and/or emotional behaviour of a subject, using the apparatus of any one of claims 1 to 31; the method comprising:

(i) presenting the subject with a first complex sensory cue at a first test locus by way of an automated presenter, and a second complex sensory cue at a second test locus by way of an automated presenter;

(ii) detecting the interaction of the subject with the first and/or second complex sensory cues; and

(iii) providing the subject with a reward following their interaction with the first complex sensory cue; but not following their interaction with second complex sensory cue;

wherein the reward is accessible to the subject at the first test locus.

33 A method for identifying a test compound and/or a risk gene that modifies the cognitive and/or emotional behaviour of a subject, using the apparatus of any one of claims 1 to 31; the method comprising:

(i) administering the subject a test compound that modifies the cognitive and/or emotional behaviour of the subject; and/or manipulating expression of a risk gene in the subject;

(ii) presenting the subject with a first complex sensory cue at a first test locus by way of an automated presenter, and a second complex sensory cue at a second test locus by way of an automated presenter;

(iii) detecting the interaction of the subject with the first and/or second complex sensory cues; and

(iv) providing the subject with a reward following their interaction with the first complex sensory cue; but not following their interaction with second complex sensory cue; wherein the reward is accessible to the subject at the first test locus; and

wherein the test compound is identified as modifying the cognitive and/or behaviour of the subject, if: the duration of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or the frequency of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or

wherein the risk gene is identified as modifying the cognitive and/or emotional behaviour of the subject, if: the duration of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control; and/or the frequency of interaction of the subject administered the test compound with the first and/or second complex sensory cues is increased or decreased, as compared to an experimental control.

34. The method of claim 33, wherein the control comprises:

(i) a reference value;

(ii) a subject administered a placebo agent, and not a test compound capable of modifying the cognitive behaviour of the subject;

(iii) a subject administered a test compound that is known not to modify the cognitive and/or emotional behaviour of said subject;

(iv) a subject administered a pharmacologically active agent that is known to modify the cognitive behaviour and/or emotional of said subject; and/or

(v) a subject not having manipulated expression of the risk gene.

35. A method for assembling the apparatus of any one of claims 1 to 31, the method comprising:

(i) joining the first substrate configured as to be distinguished by the subject in the somatosensory domain to an automated presenter, configured as to present a complex sensory cue to the subject at a first test locus; and/or

(ii) joining the second substrate configured as to be distinguished by the subject in the somatosensory domain to an automated presenter, configured as to present a complex sensory cue to the subject at a second test locus;

wherein the test apparatus further comprises:

(iii) an actuatable reward dispenser, configured as to dispense a reward to the subject; and

wherein the apparatus is configured as to permit movement of the subject between the first test and second test loci; and

wherein the substrates are configured as to be distinguished, by the subject, in the somatosensory domain.

36. Use of an apparatus according to any one of claims 1 to 31 in a method according to any one of claims 32 to 35.

37. A kit of parts, comprising:

(i) the apparatus for assessing the cognitive behaviour of a subject of any one of claims 1

to 31; and

(ii) one or more substrates configured as to be distinguished by the subject by the subject in the somatosensory domain.

5

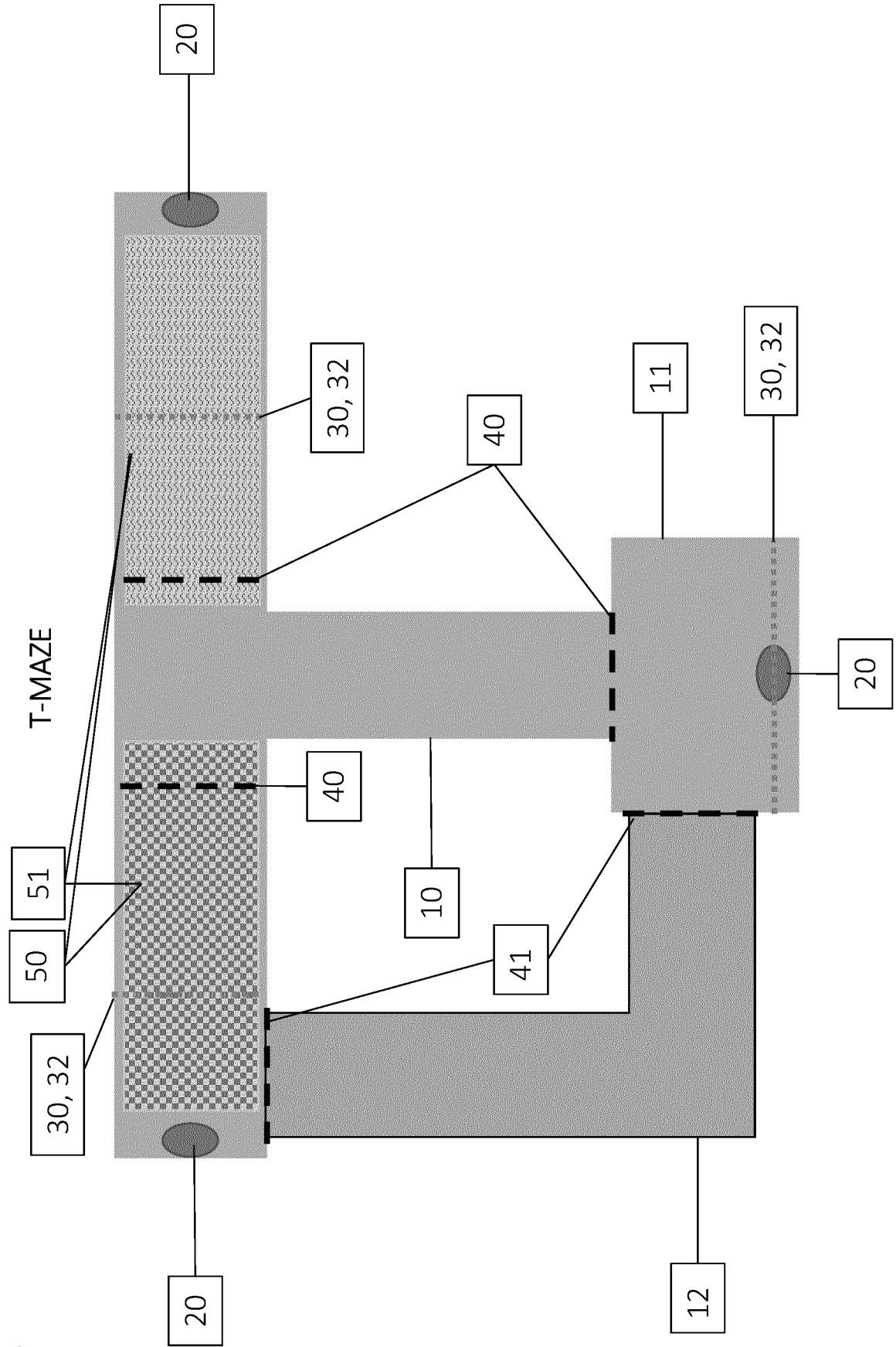


Figure 1

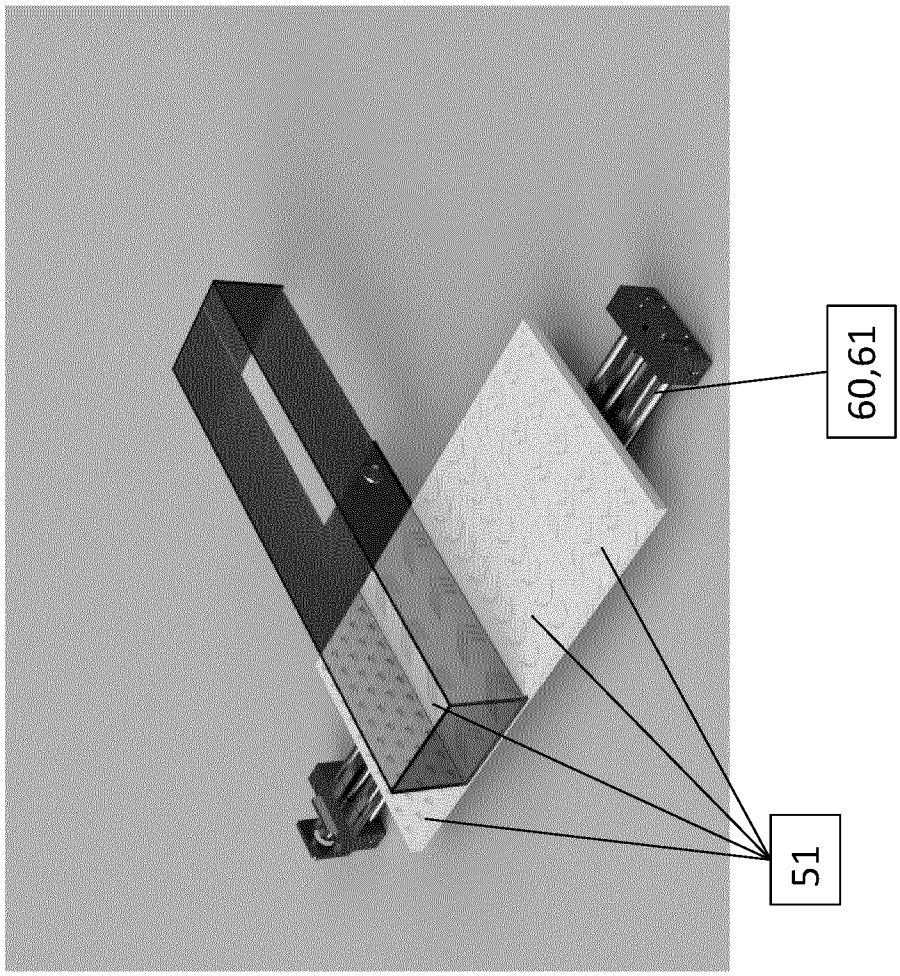


Figure 2

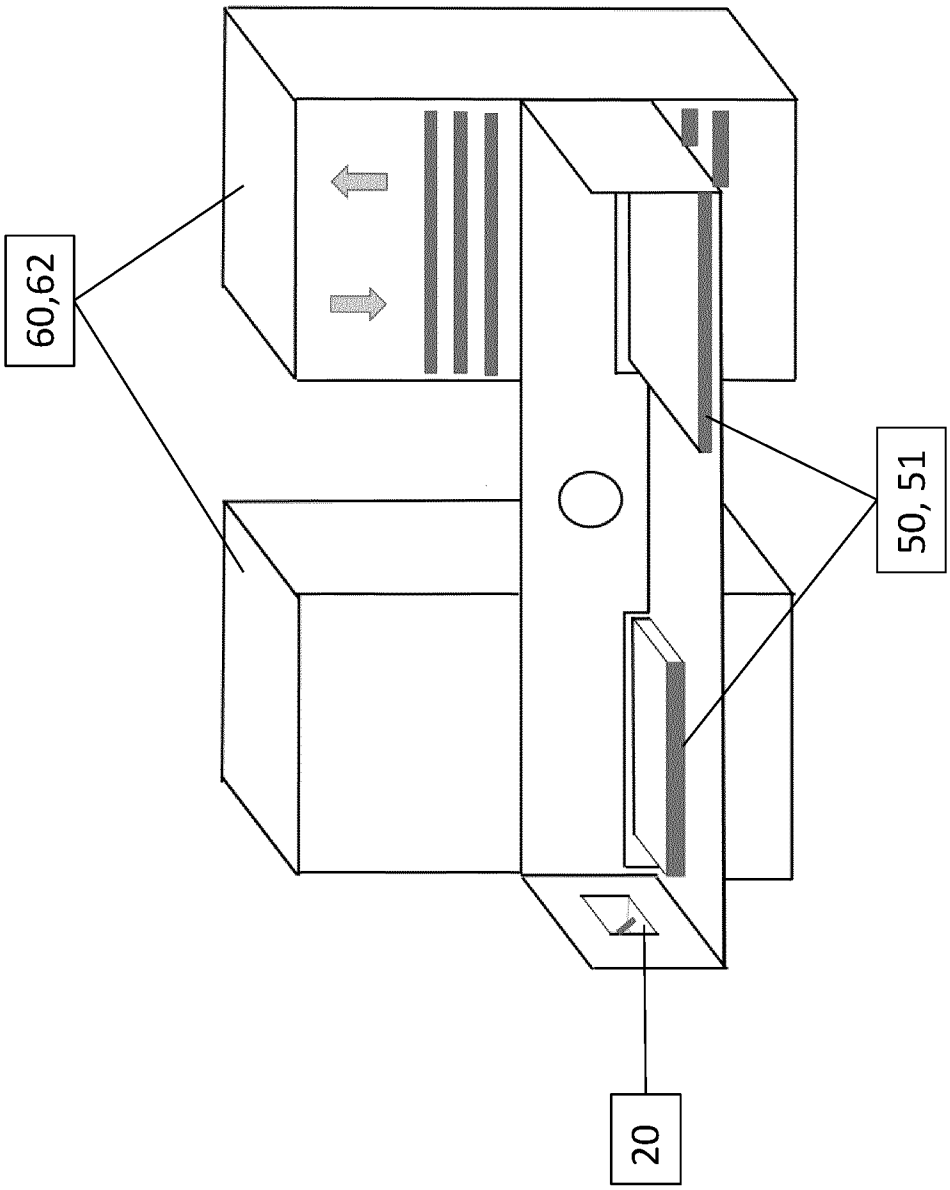


Figure 3

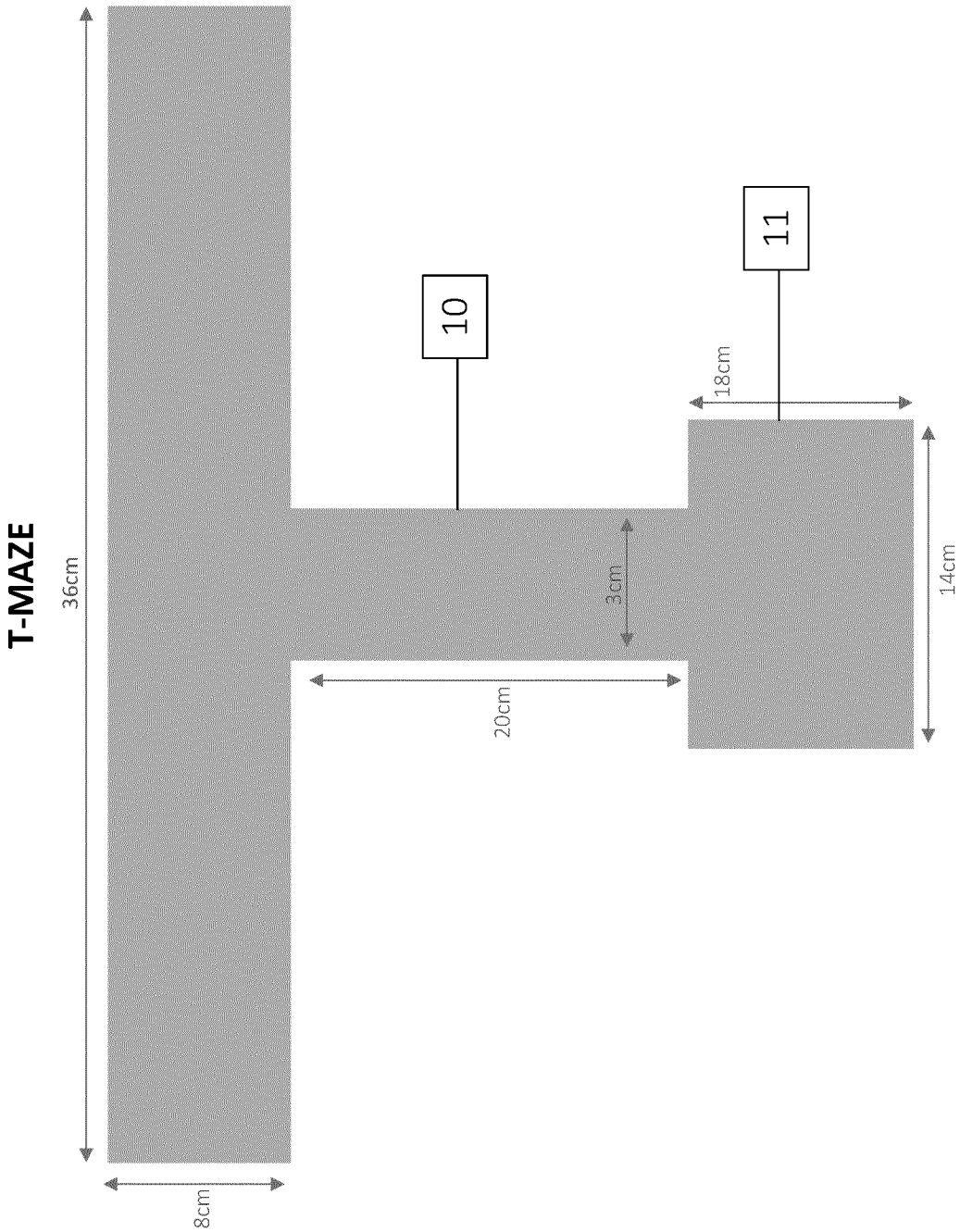


Figure 4

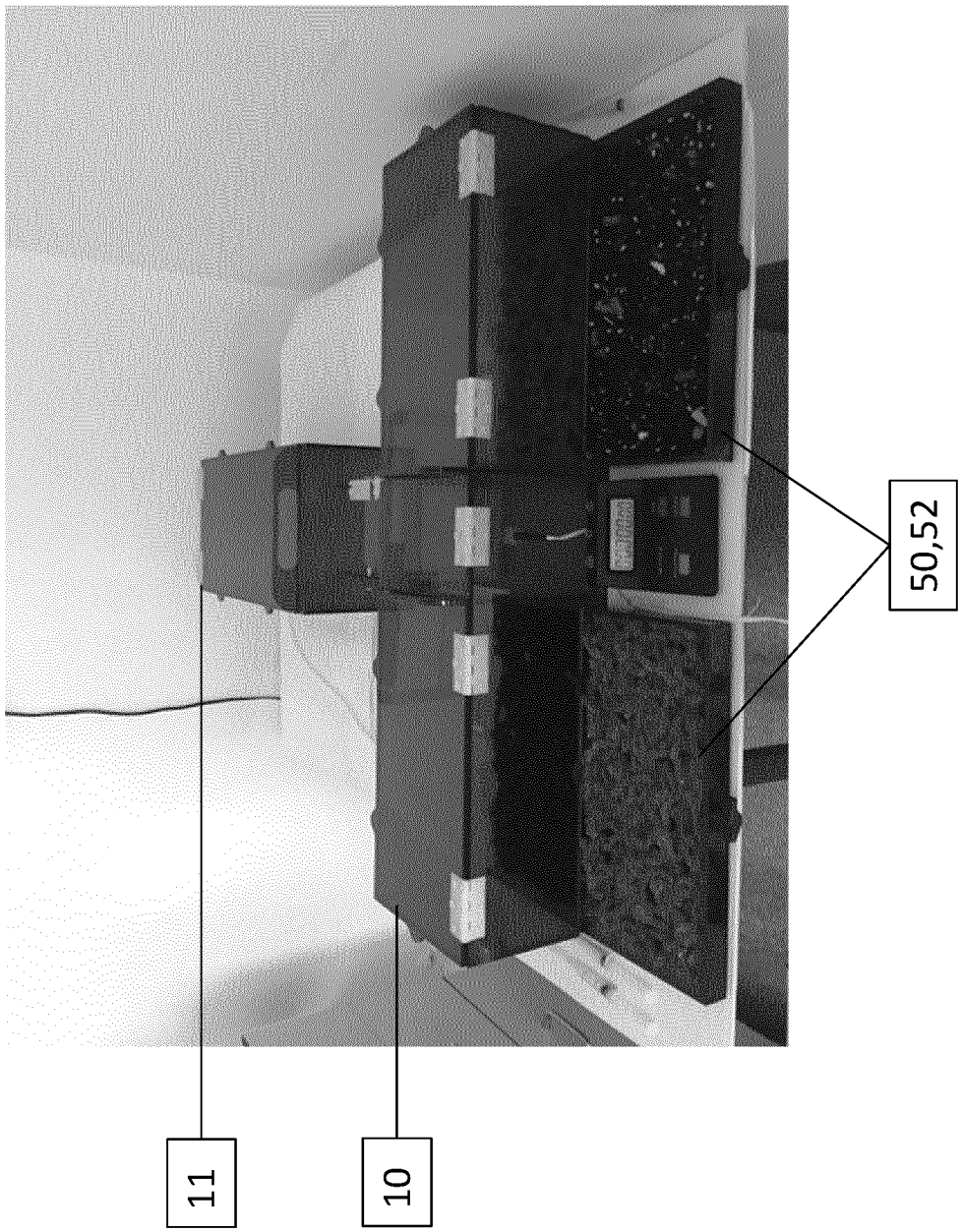


Figure 5

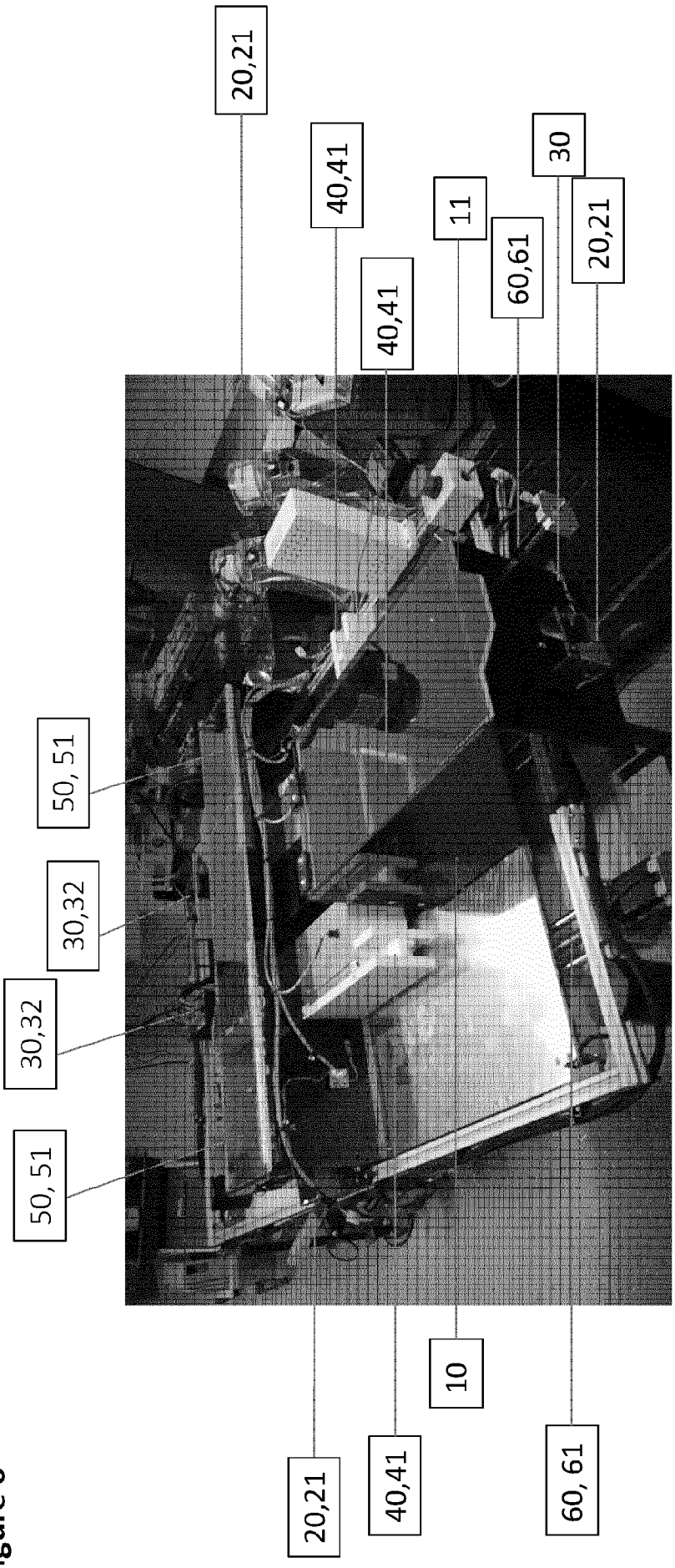

20,21
40,41
40,41
11
60,61
30
20,21
50, 51
30,32
30,32
50, 51
20,21
40,41
10
60, 61

Figure 6

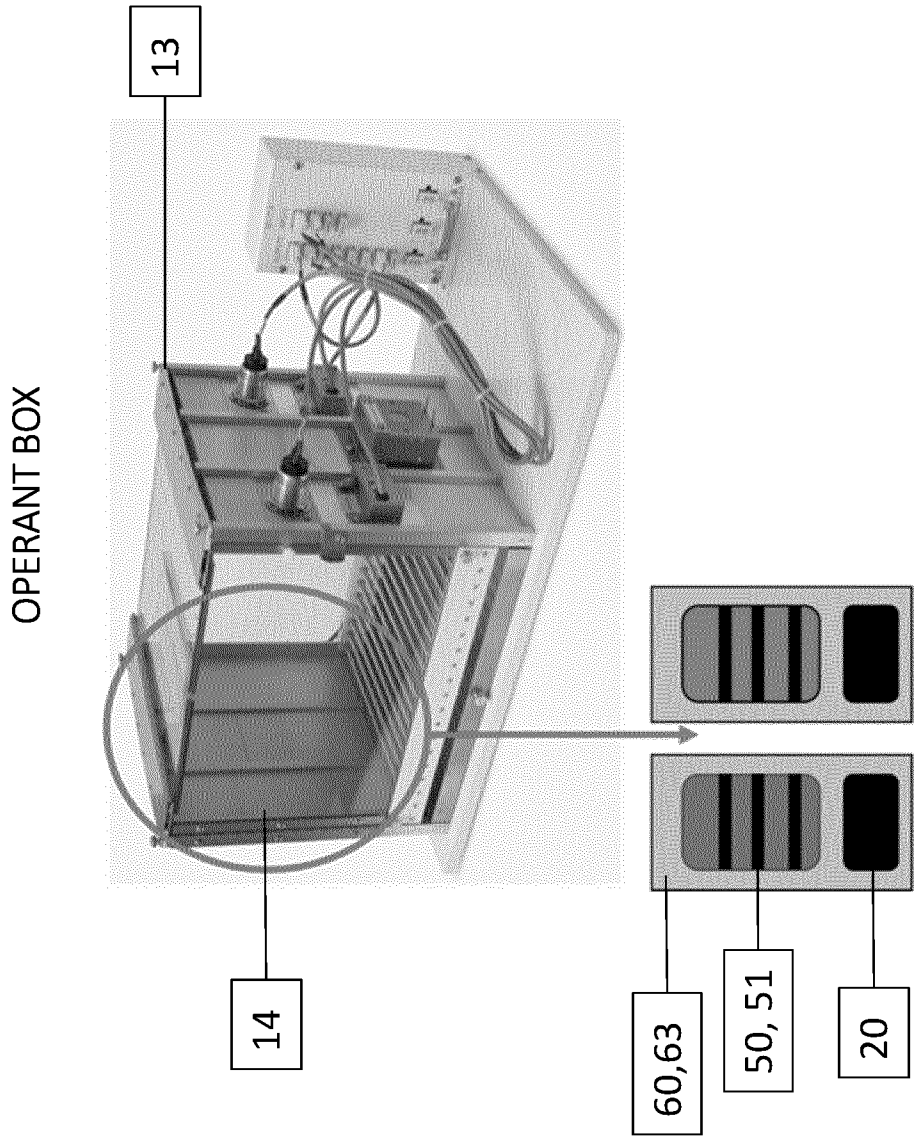


Figure 7

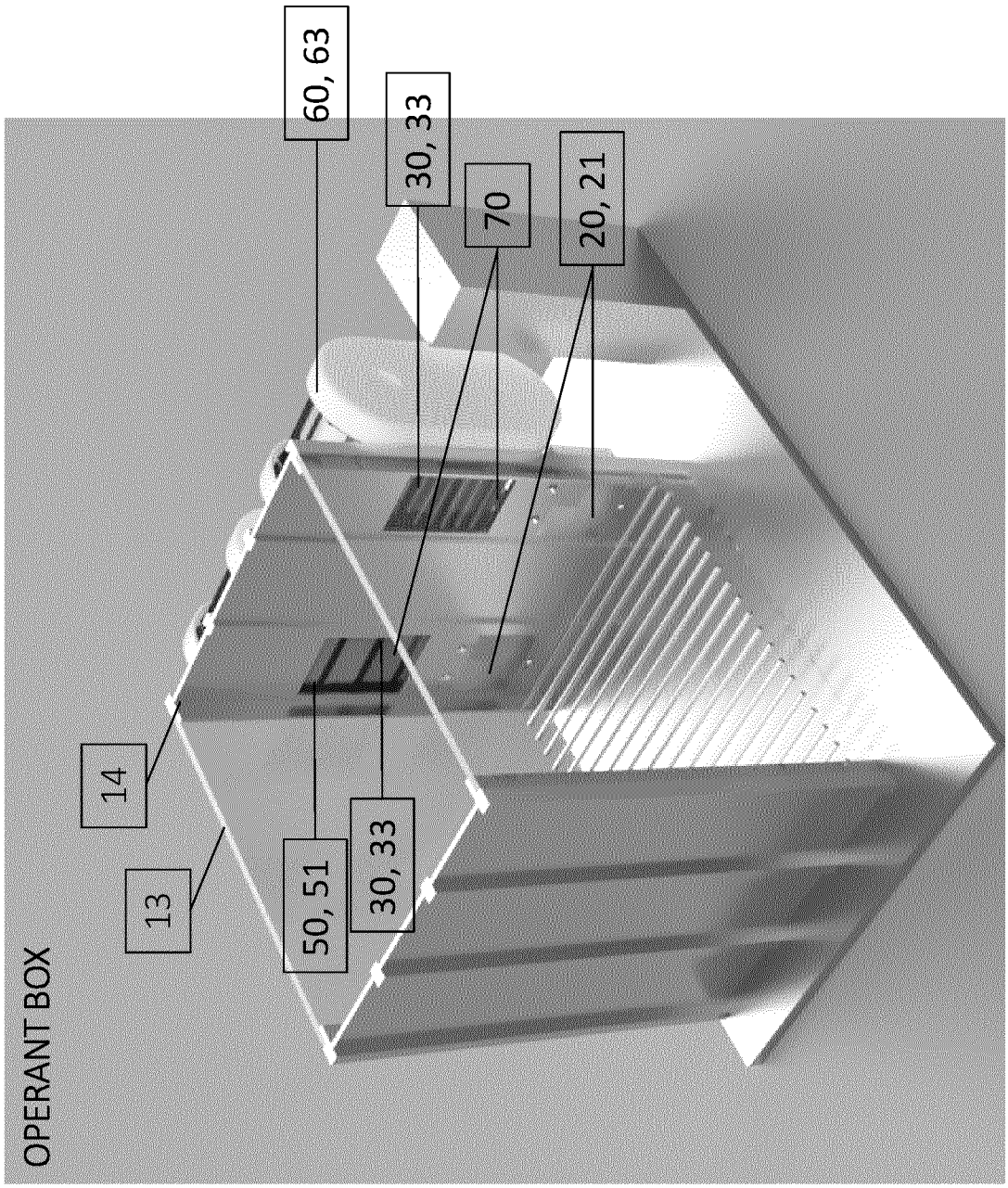


Figure 8

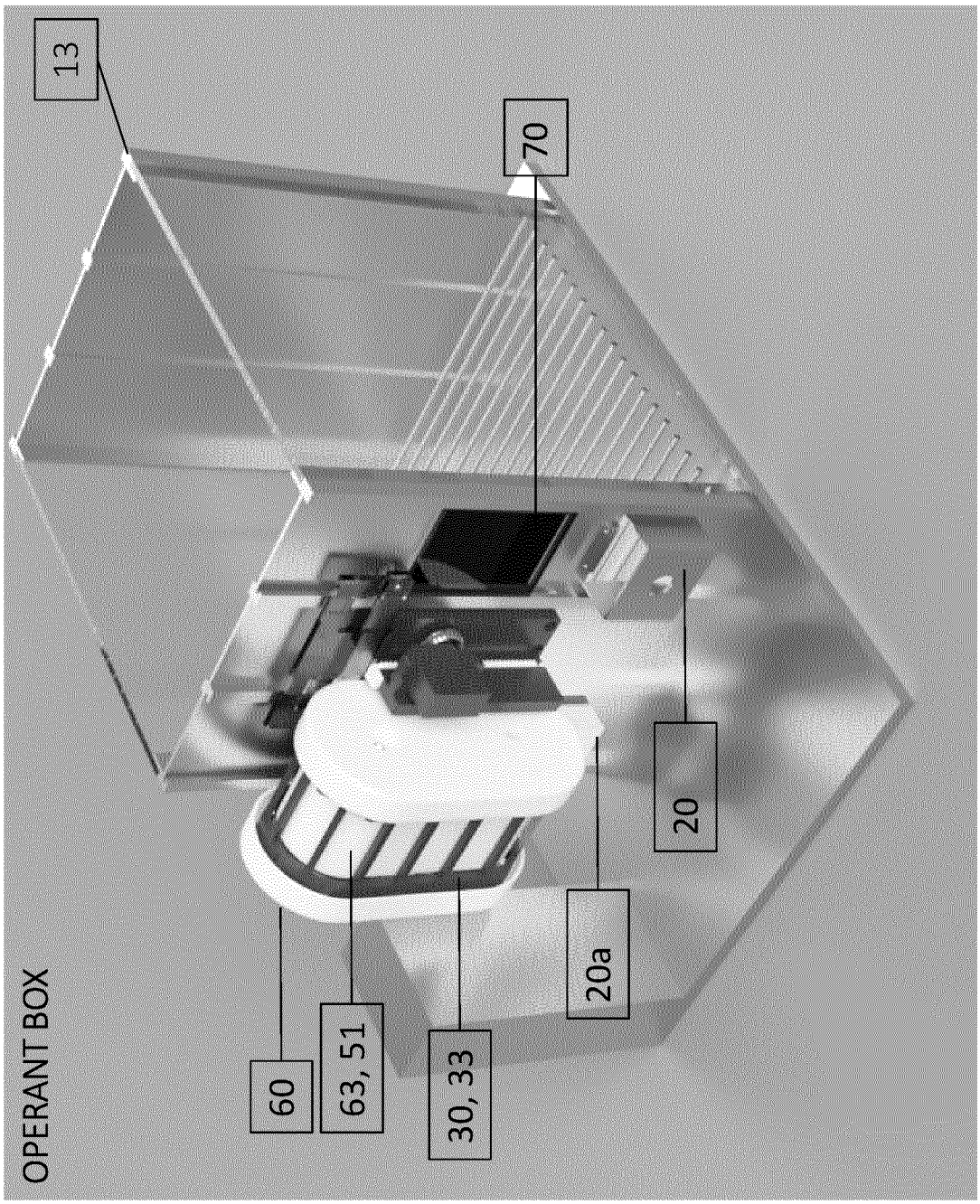


Figure 9

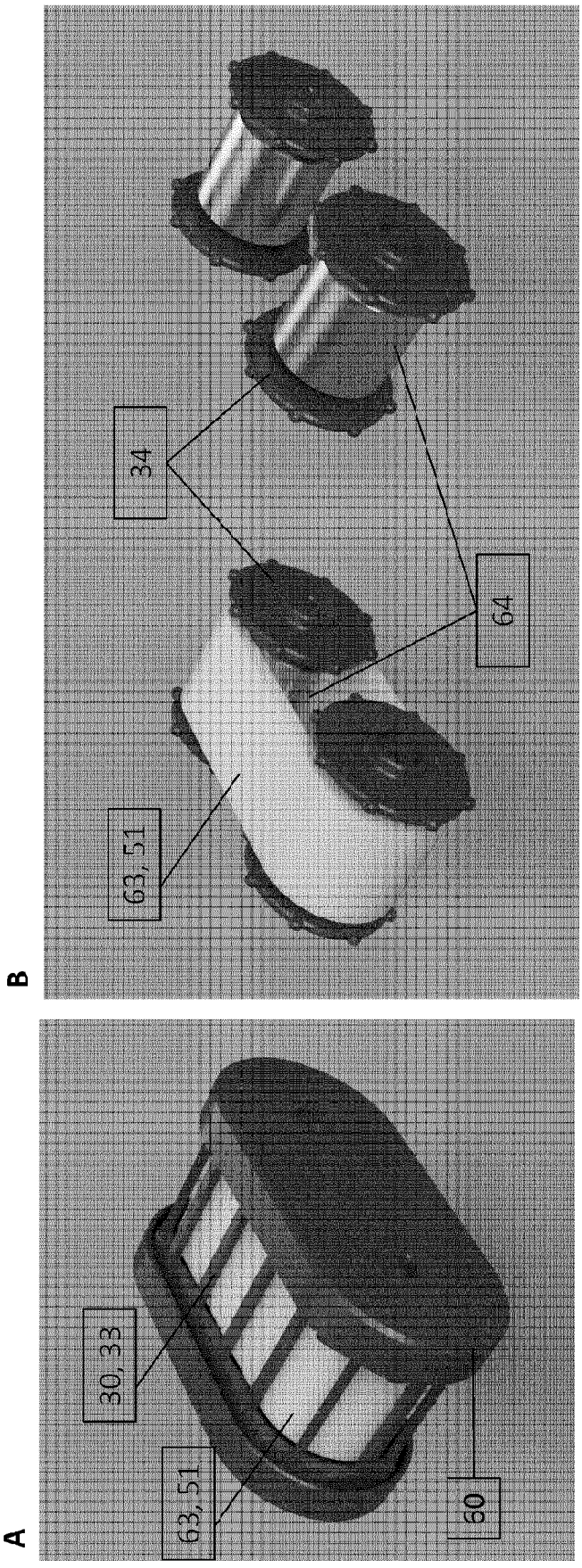


Figure 10

Figure 11

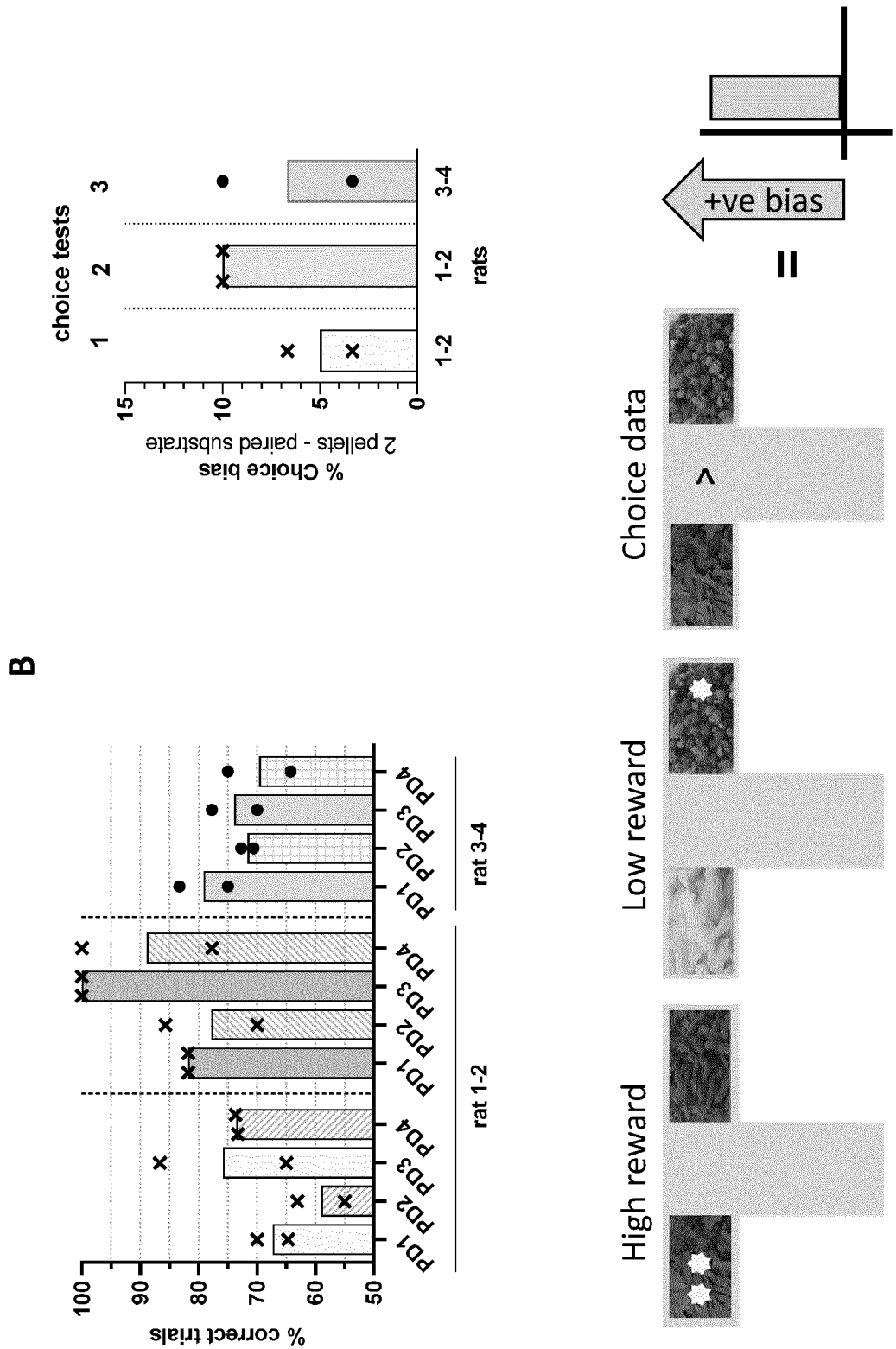
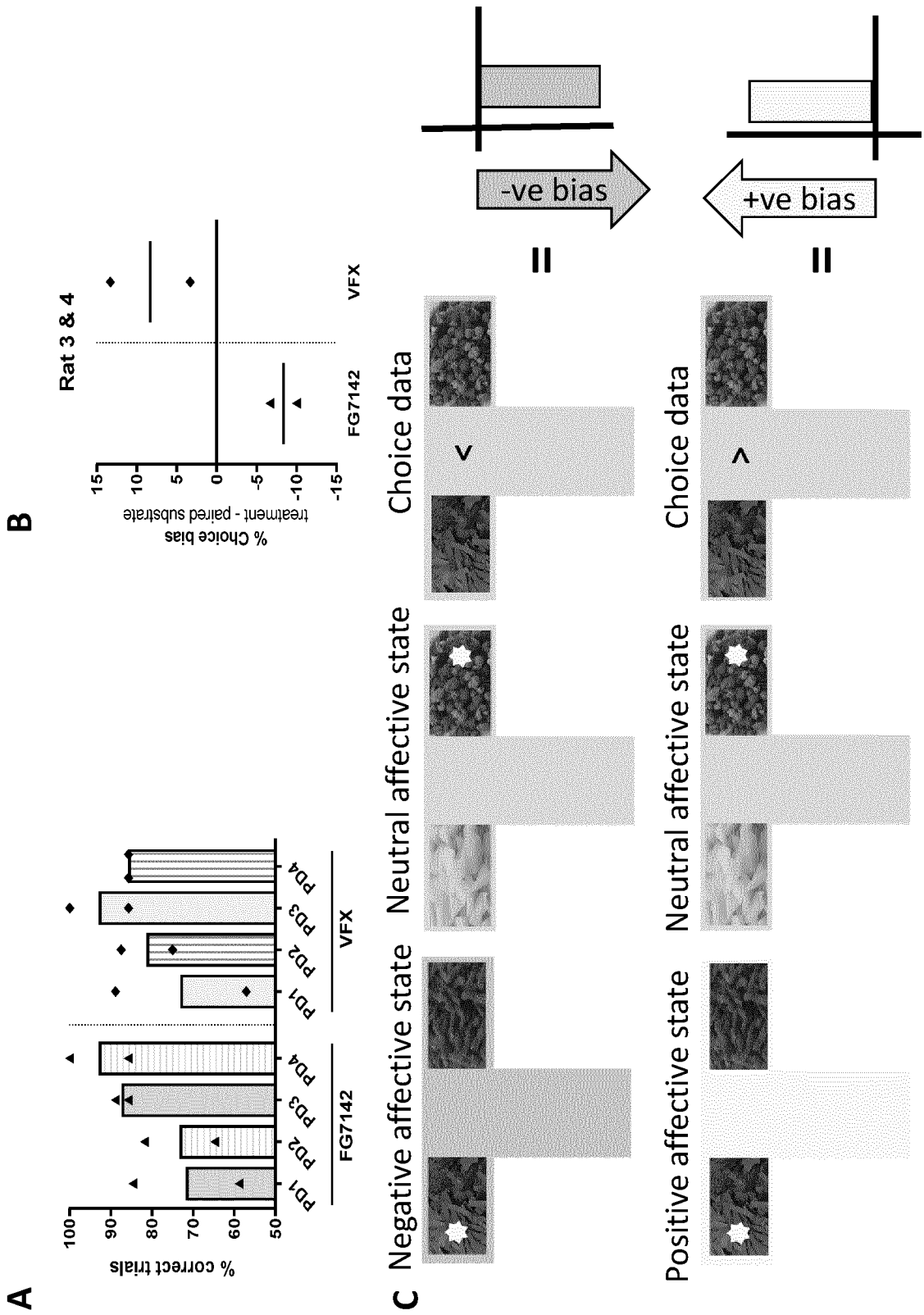

A
% correct trials
100
90
80
70
60
50
PD1 PD2 PD3 PD4 PD1 PD2 PD3 PD4
rat 1-2
PD1 PD2 PD3 PD4
rat 3-4
B
% Choice bias
2 pellets - paired substrate
15
10
5
0
choice tests
1
2
3
1-2
1-2
3-4
rats
C
High reward
Low reward
Choice data
>
+ve bias
=

Figure 12


A
% correct trials
100
90
80
70
60
50
PD1
PD2
PD3
PD4
FG7142
PD1
PD2
PD3
PD4
VFX
B
Rat 3 & 4
% Choice bias
treatment - paired substrate
15
10
5
0
-5
-10
-15
FG7142
VFX
C
Negative affective state
Neutral affective state
Choice data
-ve bias
Positive affective state
Neutral affective state
Choice data
+ve bias

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/062352

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/16
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/180731 A1 (GARNER JOSEPH P [US] ET AL) 19 July 2012 (2012-07-19) paragraphs [0046], [0064], [0088], [0092] - [0103]	1-37
A	MCBRIDE SEBASTIAN D ET AL: "A mobile, high-throughput semi-automated system for testing cognition in large non-primate animal models of Huntington disease", JOURNAL OF NEUROSCIENCE METHODS, ELSEVIER SCIENCE PUBLISHER B.V., AMSTERDAM, NL, vol. 265, 29 August 2015 (2015-08-29), pages 25-33, XP029527268, ISSN: 0165-0270, DOI: 10.1016/J.JNEUMETH.2015.08.025 figures 1-3	2,21

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2024	22/07/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kronberger, Raphael

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/062352

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 409 685 B1 (MERZENICH MICHAEL MATHIAS [US] ET AL) 25 June 2002 (2002-06-25) figures 4,5	25
A	US 2019/343071 A1 (TROTTIER LEO [US] ET AL) 14 November 2019 (2019-11-14) paragraphs [0226] - [0263]	1,21

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/062352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012180731 A1	19-07-2012	EP 2440039 A2	18-04-2012
		US 2012180731 A1	19-07-2012
		WO 2010144494 A2	16-12-2010
US 6409685 B1	25-06-2002	AU 746634 B2	02-05-2002
		CA 2277826 A1	27-05-1999
		EP 0954241 A1	10-11-1999
		JP 2001511050 A	07-08-2001
		US 6267733 B1	31-07-2001
		US 6409685 B1	25-06-2002
		WO 9925245 A1	27-05-1999
US 2019343071 A1	14-11-2019	US 2017290290 A1	12-10-2017
		US 2019343071 A1	14-11-2019
		US 2023210086 A1	06-07-2023
		WO 2016036711 A1	10-03-2016