The use of integrated behavioural z-scoring in behavioural neuroscience – A perspective article

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ABSTRACT

Complex pathophysiology in psychiatric disorders results in difficulties interpreting pre-clinical data. Guilloux et al. (2011b), proposed an integrated behavioural z-scoring procedure to improve the predictive validity of animal models by converging evidence similarly used to diagnose mental health conditions in humans. Here, I set out to give a brief review of the current methodology and literature using integrated behavioural z-scoring. Secondly, I will discuss the benefits and downfalls of integrated behavioural z-scoring and its potential future applications. Integrated behavioural z-scoring is a methodology used most frequently within animal models of depression and anxiety. Here, I am suggesting broadening the application of integrated behavioural z-scoring beyond the field of depression and anxiety to a three-step methodology to obtain disease-specific behavioural z-scores (i.e. Schizophrenia index, Alzheimer’s disease index) to aid translatability and interpretation of data. Lastly, I suggest integrating not only behaviour but also biological variables to create converging psychological and physiological evidence to sustain face and construct validity, while improving predict validity.

1. Introduction

Human behaviour can be modelled in animals using comprehensive behavioural test batteries investigating the entirety of phenotypic features resembling the disorder in humans (Bovenkerk and Kaldewaij, 2014). Animal models are a useful tool to investigate the pathophysiology, psychopathology and potential novel treatments for psychiatric disorders (Bovenkerk and Kaldewaij, 2014). Although behavioural testing can allow researchers to measure multiple disease phenotypes (observable characteristic influenced by genetics and environmental factors (Bearden et al., 2016)), variability between animals and differing experimental testing conditions, such as time of the day (Bailey et al., 2006; Roedel et al., 2006), experimenter and handling (Bailey et al., 2006; Bohlen et al., 2014), housing conditions (Bailey et al., 2006; Balcombe, 2006), sex (Georgiou et al., 2022) and age (Shoji et al., 2016) of the animal might result in altered outcomes called behavioural noise (Guilloux et al., 2011b). Behavioural noise or variability can result in difficulty interpreting data. This variability led Guilloux et al. (2011b) to suggest an integrated behavioural z-scoring technique to comprehensively analyse anxiety- and depressive-like states in mice using complementary tests which include a battery of behavioural tests investigating similar behavioural phenotypes (Guilloux et al., 2011b).

Z-scores are standard scores, which represent the number of standard deviations a score is above or below the mean outcome score (Andrade, 2021). By standardising the distribution, comparisons can be made across different variables (Andrade, 2021). A z-score is obtained by subtracting the population mean from a single raw score. This difference is then divided by the population standard deviation (Labots et al., 2018). Consequently, Guilloux et al. (2011) used this technique to normalise multiple behavioural tests of paradigms (complementary tests), into a single emotionality z-score index. This methodology proposed by Guilloux et al. (2011b) relies on converging evidence similarly used to diagnose mental health conditions in humans, to standardise complex pathophysiology into a single paradigm. An example in human medicine of converging evidence is the medical scale used in individuals with schizophrenia to measure symptom severity, Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This scale investigates positive, negative symptoms and general psychopathology. These individual symptom scores can then be combined to assess overall symptom severity (Leucht et al., 2005).

Within this review, I will provide a brief overview of the current methodology of integrated behavioural z-scoring and literature using integrated behavioural z-scoring in rodent studies. Then, I will be discussing the benefits and downfalls of an integrated behavioural z-
scoring and the potential future directions of this methodology.

2. Methodology

2.1. Eligibility & inclusion criteria

I investigated original articles using integrated behavioural z-scoring within the manuscript. To be included studies had to use z-scoring on original, complementary behavioural data in rodent models. No date or language restriction was applied. As this publication is based on Guiloux et al. (2011b), I included studies, which cited this publication and the publications itself.

2.2. Database search strategy

The databases used were Pub Med and Scopus additional records were identified by scanning the reference list and ResearchGate. The final search was performed on 21/06/2022.

2.3. Report selection

The author (AKK) determined the eligibility of papers by screening titles, abstracts, and methodology for relevance. Eligible documents were then read as a whole to analyse if the articles matched the inclusion criteria. Excluded articles were documented, and reasons were given for exclusion.

2.4. Data extraction

AKK extracted information from relevant publications including the area of research, animal model/paradigm, year of publication, behavioural test, behaviours integrated and naming of z-score/index by individual publications.

3. Results

3.1. Database search

The initial search resulted in 252 results including the original publication by Guiloux et al. (2011b). Duplicates (n = 91) were excluded resulting in 161 records being screened for eligibility. During eligibility screening, 61 additional articles were excluded, as 17 articles were not original research articles (Review (n = 13), Book chapter (n = 1), Protocol (n = 2), JOVE Video (n = 1)), and 32 articles did not perform integrated behavioural z-scoring and seven articles did not perform z-scoring on behavioural analysis, four studies were excluded as they did not conduct behavioural testing in rodents and one full text could not be obtained. This search process resulted in 100 articles being included in this review (Fig. 1).

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Fig. 1. Flow diagram.
4. Main section

4.1. A brief overview of the current methodology

Integrated behavioural z-scoring was first proposed by Guilloux et al. (2011b) to comprehensively analyse anxiety- and depressive-like states in mice using complementary tests to reduce behavioural noise (Guilloux et al., 2011b). Complementary tests, a battery of behavioural tests relating to similar emotional states, are based on the core symptoms evaluated in the human depression scales (Guilloux et al., 2011b).

All publications, identified within this review had the same goal as the Guilloux et al. (2011b) publication, however, some varying methodologies can be identified. Within this section, we will be identifying the different methodologies.

In the original publication by Guilloux et al. (2011b) z normalisation was calculated by subtracting the observed parameter (X) from the group’s mean(μ), which is then divided by the population’s standard deviation (σ).

$$z = \frac{X - \mu}{\sigma}$$

The results of this equation will indicate how many standard deviations an individual is above or below the mean of the control population. The directionality of the scores will need to be adjusted according to the integrated behavioural variable. This means, for example, that when investigating social behaviour with individual variables we must decide if all variables share the same directionality. In a social behavioural paradigm, one might investigate, sniffing behaviour (social behaviour), or avoidance behaviour (anti-social behaviour). This variable directionality needs to be adjusted when using behavioural z-scoring that in this example decreased avoidance behaviour was interpreted as increased social behaviour (Kraeuter et al., 2020).

To obtain an integrated behavioural z-score the individual z-scores of each animal from each test are added and divided by the number of tests included in the analysis.

Overall Integrated behavioural $z$-score = \( \frac{Z_{test1} + Z_{test2} + Z_{test3} + \ldots}{\text{Number of Tests}} \)

This overall integrated behavioural $z$-score can then be averaged for all animals per group to obtain mean and standard deviations for graphical group representation. Z-score data can then be used statistically for further analysis of significance.

Another method based on the aforementioned methodology by Guilloux et al. (2011b) was proposed by Labots et al. (2018). This methodology was proposed as the original methodology by Guilloux et al. (2011b) did not account for studies, which do not have an identifiable reference or control group, such as sex and strain differences studies. Secondly, the originally proposed methodology would be impossible, if the control group would have a standard deviation of zero (Labots et al., 2018). Labots et al. (2018) follow a similar methodology to Guilloux et al. (2011b), however, instead of using a single reference group, Labots et al. (2018) used the pooled data of all groups as a reference, which will further decrease the chance of a standard deviation of zero.

4.2. Results: review of the current literature using z-scores

Integrated behavioural z-scoring has increasingly been used since the first publication by Guilloux et al. (2011b) from three publications in 2011–21 publications in 2021 (Fig. 2). Although the use of integrated behavioural $z$-scoring has increased (Fig. 2) the majority of research (64%) has not deviated from the original field of research by Guilloux et al. (2011b) on major depressive and or anxiety disorder (Fig. 3).

The 100 publications included in this literature review (Table 2) have computed 152 integrated $z$-scores (Table 1). The majority of $z$-scores computed were the “Emotionality z-score/index” (33%) originally proposed by Guilloux et al. (2011b) other common (above 5%) integrated behavioural $z$-scores computed include: “Locomotion $z$-score/index” (11%), “Anxiety $z$-score/index” (13%) and “Depression $z$-score/index” (6%) (Table 1). Note this table is summary of information presented in Table 2. The number of behavioural tests and subsequently behaviours integrated varied within integrated behavioural $z$-scores. To demonstrate, 50 “Emotionality $z$-score/index” were computed across the publications reviewed with most publications integrating 4 (1–8) different behavioural tests and integrating 6 (2–12) behaviours. The most common behavioural tests integrated for an “Emotionality $z$-score/index” were the open field test (OF), elevated plus maze (EPM), tails suspension test (TST), forced swim test (FST), novelty suppression of feeding (NSF), sucrose preference test (SPT), splash test (ST), coat condition (Coat), PhenoTyper test and light dark box (LD) (Table 1).

4.3. Discussion: benefits and downsfalls of an integrated behavioural $z$-scoring

Thus far integrated behavioural $z$-scoring has not been used extensively across different areas of research (Fig. 3, Table 1). Within this section of the review, I will be discussing the benefits and downsfalls of behavioural $z$-scoring and comparing $z$-scoring to alternative methods used.

Integrated behavioural $z$-scoring allows for improved interpretation of behavioural data, by normalising data with different scales to one scale (Guilloux et al., 2011b). Furthermore, as mentioned previously behavioural testing can create great variability or behavioural noise due to altering testing conditions and inter and between animal differences.
Table 1
Number of integrated z-scores identified within the Literature. (Summary of main findings of Table 2) The number and type of behavioural tests and behaviours vary within individual z-scores reducing reproducibility between studies. *Colour would be preferable for Table 1*.

| Integrated behavioural Z-scores | Complementary test (absolute) |
|---------------------------------|--------------------------------|
|                                  | **Total** | **Medication** | **Control** | **Behavioural** | **Real-time** | **Image analysis** |
|                                  | **NRS** | **ACE** | **RIP** | **WM** | **PhenoTyper** | **NIH** | **Cylinder** | **Geotaxis** | **Pre-pulse** | **Startle** | **FST** | **NSF** | **SPT** | **ST** | **Cookie** | **FC** | **WM** | **MWM** | **Beam** | **VPWM** | **OF** | **EPM** | **LD** | **mHB** | **NOR** | **SI** | **TST** | **FST** | **NSF** | **SPT** | **ST** | **Cookie** | **FC** | **WM** | **MWM** | **Beam** | **VPWM** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | 152             | 6               | 6               | 2               | 9               | 3               | 2               | 4               | 1               | 2               | 4               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               | 2               |

Note: maximum (max), minimum (min), open field test (OF), elevated plus maze test (EPM), light dark box test (LD), modified hole board test (mHB), social interaction test (SI), tail suspension test (TST), forced swim test (FST), novelty suppression of feeding (NSF), sucrose preference test (SPT), splash test (ST), cookie test (Cookie), fear conditioning test (FC), Working memory test (WM), Morris Water Maze (MWM), novel object recognition test (NOR), Beam walk test (Beam), visible platform water maze (VPWM), maternal behaviours (Maternal), Nest building test (Nest), Puzzle box (Puzzle), attentional set shifting task (ASST), Acoustic Startle Response (ASR), Resident Intruder test (RIT), Shock probe burying task (SPBT), Elevated zero maze (Zero), Contextual fear task (CFT), Marble burying (Marbles), Spontaneous Alternation Maze (T-maze), Restraint test (Restraint), Odour-induced sniffing behaviour (OISB), Object recognition (OR), Object Location (OL), coat state (Coat), PhenoTyper test (PhenoTyper), novelty-induced hypophagia test (NIH), cylinder test (Cylinder), negative geotaxis analysis (Geotaxis), Pre-pulse inhibition of startle (PPI), Burrowing test (Burrow), novelty-induced locomotion (NIL)

(Bailey et al., 2006; Balcombe, 2006; Bohlen et al., 2014; Georgiou et al., 2022; Roedel et al., 2006; Shoji et al., 2016). This variability can be reduced by using an integrated behavioural z-score (Guiloux et al., 2011b). An alternative to an integrated behavioural z-scoring is principal component analysis (PCA). PCA can be used to produce composite variables, which are variables made up of two or more variables, which are highly related to one another (Labots et al., 2018). PCA is less suited for behavioural data as consistent variables need to be obtained for PCA (Guiloux et al., 2011b).

Two methodologies are used to determine an integrated behavioural z-score (Guiloux et al., 2011b; Labots et al., 2018). Labots et al. (2018) demonstrated a technique to investigate cohorts, which do not have an obvious reference or control group. Investigators wanting to use integrated z-scoring need to clearly identify, which of the two above methods.
Table 2
Comprehensive Review of Current Literature using integrated z-scores.

| Area of research | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score /Index | Reference |
|------------------|-----------------------|-------------------|----------------------|----------------|-----------|
|                  |                       | Tests             | Count                |                |           |
| Major depressive | Unpredictable chronic mild stress | EPM, OF, NSF | 3 | Time in the centre (OF), distance in periphery/total distance ratio (OF), time in the open arms (EPM), open/closed arms entries ratio (EPM), latency time to eat the pellet (NSF) | 5 | Emotionality | (Guilloux et al., 2011a) |
| disorder and/or  |                       | EPM, OF          | 2 | Total crosses (OF), total crosses (EPM) | 2 | Locomotion |           |
| Anxiety          |                       |                  |                      |                |           |
|                  | Unpredictable chronic mild stress | EPM, OF, NSF, FST | 4 | Time in open arms (EPM), crosses into open arms (EPM), time in the centre (OF), distance in the centre (OF), time swimming (FST), latency to feed (NSF) | 6 | Emotionality | (Edgar et al., 2011) |
|                  |                       | EPM, OF          | 2 | Total crosses (EPM), distance travelled (OF) | 2 | Locomotion |           |
|                  | Chronic restraint stress | FST, SPT | 2 | Sucrose preference (SPT), immobility (FST) | 2 | Depression | (Huynh et al., 2011) |
|                  | Unpredictable chronic mild stress | NSF, FST, EPM, OF | 4 | Time in open arms (EPM), crosses into open arms (EPM), time in the centre (OF), distance in the centre (OF), time swimming (FST), latency to feed (NSF) | 6 | Emotionality | (Seney et al., 2012) |
|                  |                       | EPM, OF          | 2 | Total crosses (EPM), distance travelled (OF) | 2 | Locomotion |           |
|                  | Unpredictable chronic mild stress | EPM, OF | 2 | Time and crosses into the open arms (EPM), time in the centre (OF), distance in the centre (OF) | 3 | Anxiety | (Seney et al., 2013) |
|                  | Unpredictable chronic mild stress | EPM, OF, NSF, Cookie, SPT | 5 | Time in the open arms (EPM), crosses into the open arms (EPM), time in the centre (OF), distance in the centre (OF), latency to feed (NSF), latency to eat (cookie), sucrose preference (SPT) | 7 | Emotionality | (Soumier and Sibille, 2014) |
|                  | Corticosterone | EPM, TST, ST | 3 | Time in the open arm (EPM), open/open arm entries ratio (EPM), amnibulatory distance (EPM), immobility (TST), grooming duration (ST) | 5 | Emotionality | (Petit et al., 2014) |
|                  | Strain comparison | FST, TST | 2 | Latency (FST), immobility (TST), latency (TST), immobility (TST) | 4 | Depression | (de Sá-Calçada et al., 2015) |
|                  | Corticosterone | ST, TST, EPM, OF, NSF | 5 | Grooming time (ST), immobility time (ST), open arms entries (EPM), time in the open arms (EPM), centre entries (OF), time in the centre (OF), centre to total distance ratio (OF), latency to feed (NSF) | 8 | Emotionality | (Quesseveur et al., 2015) |
|                  | Genetic & Perinatal | EPM | 1 | Latency to first open arm entry (EPM), time in the open arm (EPM), open arm entries (EPM), head dips (EPM) | 4 | Anxiety | (Altieri et al., 2015) |
|                  |                       | OF | 1 | Time in the centre (OF), centre to total distance travelled ratio (OF) | 2 | Anxiety |           |
|                  |                       | EPM, OF | 2 | Arm entries (EPM), rears (EPM), distance travelled (OF) | 3 | Exploration |           |
|                  | Unpredictable chronic mild stress | EPM, OF, NSF, SPT | 4 | Time in the open arm (EPM), crosses into the open arm (EPM), time in the centre (OF), distance in the centre (OF), latency to feed (NSF), sucrose consumption (SPT) and sucrose preference (SPT) | 7 | Emotionality | (Lin and Sibille, 2015) |
|                  |                       | EPM, OF | 2 | Arm entries (EPM), distance travelled (OF) | 2 | Locomotion |           |

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| Area of research | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score /Index | Reference |
|------------------|-----------------------|------------------|----------------------|----------------|-----------|
|                  |                       |                  |                      |                |           |
| Alzheimer’s      | Genetic               | FC, VPWM, Burrow, Nest | Freezing during exploration (FC), freezing during fear-induced contextual memory (FC), freezing during tone-induced fear memory (FC), swim path (VPWM), thigmotaxis (VPWM), floating (VPWM), burrowing (Burrow), nest score (Nest) | 8 | Global performance/Total | (Janus et al., 2015) |
|                  |                       |                  |                      |                |           |
| Major depressive| Corticosterone        | OF, EPM, NSF, ST | Time in the centre (OF), entries into the centre (OF), ratio (OF), time in open arm (EPM), entries in open arm (EPM), latency to feed (NSF), grooming duration (ST) | 7 | Emotionality | (Mendez-David et al., 2017a) |
| disorder and/or |                       |                  |                      |                |           |
| Anxiety          |                       |                  |                      |                |           |
| Research Animal  | Strain difference     | mHB              | Board entries (avoidance), latency until first board entry (avoidance), time on the board (avoidance), number of risk assessments (risk assessment), latency until the first risk assessment (risk assessment), number of self-grooming (arousal), latency until first self-grooming (arousal), time spent self-grooming (arousal), number of defecations (arousal), latency until first bolus (arousal), number of urinations (arousal), latency until first urination (arousal) | 12 | Anxiety | (Labots et al., 2016a) |
| Wellbeing & Met|                       |                  |                      |                |           |
| Methodology &    |                       |                  |                      |                |           |
| Strain difference|                       |                  |                      |                |           |
| Major depressive| 60% fructose-enriched diet | OF, TST, ST, NSF | Centre entries (OF), time in the centre (OF), centre-to-total-distance ratio (OF), immobility time (TST), grooming time (ST) | 5 | Emotionality | (Zemdegs et al., 2016a) |
| disorder and/or |                       |                  |                      |                |           |
| Anxiety          |                       |                  |                      |                |           |
| Gestational/     | Gestational stress    | Maternal         | Pup retrieval, contact with pups, nest presence, anogenital licking | 4 | Z-latency | (Belnose et al., 2016) |
| Development      |                       |                  |                      |                |           |
| Major depressive| Unpredictable chronic mild stress | EPM, OFT, NSF, Cookie | Per cent crosses into open (EPM), distance travelled in the centre (OF) latency to feed (NSF), latency to bite (cookie) | 4 | Emotionality | (Piantadosi et al., 2016) |
| disorder and/or |                       |                  |                      |                |           |
| Anxiety          |                       |                  |                      |                |           |
| Light regime     | mHB, LD, EPM          |                  | Board entries (mHB), latency until first board entry (mHB), time on the board (avoidance), light compartment entries (LD), latency until first light compartment entry (LD), time spent in the light compartment (LD), open arm entries (EPM), latency until the first visit to the open arm (EPM), time spent in the open arms (EPM), number of risk assessments (mHB), latency until the first risk assessment (mHB), number of stretched attands (EPM), latency until first stretched attend (EPM) | 13 | Anxiety | (Labots et al., 2016b) |
|                  |                       |                  |                      |                |           |
|                  | mHB, LD, EPM          |                  | Board entries (mHB), latency until first board entry (mHB), time on the board (avoidance), light compartment entries (LD), latency until first light compartment entry (LD), time spent in the light compartment (LD), open arm entries (EPM), latency until the first visit to the open arm (EPM), time spent in the open arms (EPM), number of risk assessments (mHB), latency until the first risk assessment (mHB), number of stretched attands (EPM), latency until first stretched attend (EPM) | 9 | Avoidance |           |

(continued on next page)
| Area of research           | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score /Index | Reference |
|---------------------------|-----------------------|-------------------|-----------------------|----------------|-----------|
|                           |                       | Tests             | Count                 |                |           |
|                           |                       | the open arm (EPM), time spent in the open arms (EPM) | Count |                  |           |
|                           |                       | Number of risk assessments (mHB), latency until the first risk assessment (mHB), number of stretched attends (EPM), latency until first stretched attend (EPM) | 4 | Risk Assessment |           |
|                           |                       | Number of self-grooming (mHB), latency until first self-grooming (mHB), time self-grooming (mHB), number of defecations (mHB), latency until first bolus (mHB), number of urinations (mHB), latency until first urination (mHB), number of self-grooming (EPM), latency until first self-grooming (EPM), time spent self-grooming (EPM), number of bolus (EPM), latency until first bolus (EPM), number of urinations (EPM), latency until first urination (EPM) | 14 | Arousal |           |
|                           |                       | Number of rearing in the box (mHB), latency until first rearing in the box (mHB), number of rearing on the board (mHB), latency until first rearing on the board (mHB), number of hole explorations (mHB), latency until first hole exploration (mHB), number of hole visits (mHB), latency until first hole visit (mHB), number of end arm explorations (EPM), latency until first end arm exploration (EPM), number of rearing in the open arm (EPM), latency until first rearing in the open arm (EPM), number of head dips (EPM), latency until first head dip (EPM) | 14 | Exploration |           |
|                           |                       | Number of line crossings (mHB), latency until first line crossing (mHB), arm entries (EPM), closed arm entries (EPM) | 4 | Locomotion |           |
| Major depressive disorder and/ | Unpredictable chronic mild stress | OF, FST | 2 | Latency to first immobility (FST), time immobile (FST), time in the centre (OF), relative centre activity (OF), number of square (OF) latency to feed (NSF), cumulative immobility (TST), sucrose preference (SPT) | 5 | Emotionality | (Shepard et al., 2016) |
| Anxiety                   |                       |                   |                       |                |           |
| Major depressive disorder and/ | Chronic social isolation | NSF, TST, SPT | 3 | Problem solving abilities trials T5 and T8 (puzzle), short term memory including trials T3, T6 and T9 (puzzle box), set shifting including IDS1 and EDS (ASST), reversal including R and IDS3R (ASST), number of sessions needed to reach the criterion of success during the training (T-maze), delayed alternation phases (T-maze) | 11 | Working Memory | (Shepard et al., 2017) |
| Cognitive Decline         | No model              | Puzzle, ASST, T-Maze | 3 | Number of grooming bouts (OF), number of rearing bouts (OF), number of crossing (OF), | 5 | Emotionality | (Wang et al., 2017) |
| Major depressive disorder and/ | High fat diet          | OFT, TST, FST     | 3 |                       |           |           | (continued on next page) |
| Area of research                  | Animal model paradigm          | Behavioural tests     | Behaviours integrated                         | Z-score /Index | Reference                                      |
|----------------------------------|--------------------------------|-----------------------|-----------------------------------------------|----------------|-----------------------------------------------|
|                                  |                                |                       | Behaviours (Test)                              | Count          |                                               |
|                                  |                                |                       | Count                                         |                |                                               |
| Major depressive disorder and/   | Corticosterone                 | EPM, NSF, ST          | immobility time (TST), immobility time (FST)  | 3              | 5 Emotionality                                 |
| Anxiety                          |                                |                       | Time in the open arms (EPM), per cent survival |                | (Mendez-David et al., 2017a)                   |
|                                  |                                |                       | (NSF), food consumption (NSF), grooming duration (ST) |                |                                               |
| Major depressive disorder and/   | Corticosterone & Chronic       | OF, EPM, NSF, ST      | Time in the centre (OF), number of entries in centre (OF) | 4              | 7 Emotionality                                 |
| Anxiety                          | Mild Stress                    |                       | distance ratio (OF), time in the open arms (EPM) |                | (Mendez-David et al., 2017b)                   |
|                                  |                                |                       | entries ratio (EPM), grooming duration (ST), latency to seed (NSF) |                |                                               |
| Alzheimer’s disease              | Genetic                        | OF, T-Maze, ASR       | Distance (OF), perimeter vertical counts (OF), number of arm entries (T-Maze) | 3              | 5 Psychosis-associated                         |
|                                  |                                |                       | distance in centre (OF), ASR (Post) (ASR)     |                | (Krivinko et al., 2017)                        |
| Major depressive disorder and/   | Predator odour stress          | extended OF, EPM,     | Relative open arm entries (EPM), open arm duration (EPM), centre duration (OF), entry rate to centre (OF), number of movements in centre (OF), thigmotaxis rate (OF), thigmotaxis latency (OF), thigmotaxis duration (OF), startle amplitudes | 3              | 9 Emotionality                                 |
| Anxiety                          |                                | Startle amplitude     |                                               |                | (Joshi et al., 2017)                           |
| Major depressive disorder and/   | Corticosterone                 | OF, EPM, NSF, ST      | Time in the centre (OF), distance ratio (OF), time in the open arms (EPM) | 4              | 6 Emotionality                                 |
| Anxiety                          |                                |                       | entries ratios (EPM), latency to feed (NSF), grooming duration (ST) |                | (Mekiri et al., 2017)                         |
| Major depressive disorder and/   | Chronic variable stress        | LD, OF, SPT, TST, FST | Time in the lit compartment (LD), number of entries into the light (LD), time spent in the centre (OF), sucrose preference (SPT), immobility (TST & FST). | 5              | 6 Emotionality                                 |
| Anxiety                          |                                |                       |                                               |                | (Scheich et al., 2017)                         |
|                                  |                                | OF, LD                | Time spent moving (OF), number of crossed fields (OF), number of peeks into the light (LD) | 2              | 3 Locomotion                                   |
| Major depressive disorder and/   | Unpredictable chronic mild     | OF, EPM, NSF, FST, SPT| Time in the centre (OF), distance in the centre (OF), number of entries in the open arms (EPM), latency to feed (NSF), immobility (FST), sucrose preference (SPT) | 5              | 6 Emotionality                                 |
| Anxiety                          | stress                         |                       |                                               |                | (Malsuch et al., 2017)                         |
| Fragile X mental retardation     | Chemogenic Inhibition          | OF, LD, EPM           | Time spent in the centre (OF), time spent in the light chamber (LD), time in open arms (EPM) | 3              | 3 Emotionality                                 |
| syndrome                         |                                |                       |                                               |                | (Khlghatyan et al., 2018)                      |
|                                  |                                | OF, LD                | Distance travelled (LD), distance travelled (OF) | 2              | 2 Locomotion                                   |
| Major depressive disorder and/   | Chronic variable stress        | OF, EPM, FST          | Time spent in the periphery (OF), time spent in the open arms (EPM), time spent in closed arms distance (EPM), time immobile (FST) | 3              | 5 Emotionality                                 |
| Anxiety                          |                                |                       |                                               |                | (Simard et al., 2018)                          |
| Major depressive disorder and/   | Chronic variable stress        | OF, EPM, FST          | Time immobile (FST), time in centre (OF), proportion peripheral distance (OF), time in the open arms (EPM), proportion closed distance (EPM) | 3              | 5 Emotionality                                 |
| Anxiety                          |                                |                       |                                               |                | (Simard et al., 2018)                          |
| Major depressive disorder and/   | Unpredictable chronic mild     | EPM, OF, FST, NSF, SPT, Cookie | Distance in the centre (OF), centre entries (OF), time spent in the centre (OF), time immobile (FST), sucrose consumption (SPT), latency to approach (NSF), latency to feed (NSF), latency to bite | 6              | 11 Emotionality                                |
| Anxiety                          | stress                         |                       |                                               |                | (Nikolova et al., 2018)                        |
| Area of research                                      | Animal model paradigm       | Behavioural tests               | Behaviours integrated                              | Z-score/Index | Reference                                       |
|------------------------------------------------------|-----------------------------|--------------------------------|---------------------------------------------------|---------------|------------------------------------------------|
| Major depressive disorder and/ Anxiety               | Chronic mild stress         | RIT (Aggression Index),        | Attack latency (RIT), time of offensive aggression (RIT), time freezing (SPBT), latency to bury from both the Acquisition and Recall Trials (6 endpoints in total) (SPBT), immobility times across the three trials (repeated FST) | 13            | Coping (Fisher et al., 2018)                   |
|                                                      |                             | SPBT, repeated FST            |                                                    |               |                                                |
| Major depressive disorder and/ Anxiety               | Unpredictable chronic mild stress | SPT, TST, LD                  | Sucrose preference index (SPT), immobility time (TST), time in light (LD) | 3             | Depression (Apazoglou et al., 2018)            |
| Posttraumatic stress disorder                        | Electric foot shock         | CFT, EPM, OF                  | Time in open arm (EPM), open arm entries/ total arm entries (EPM), central area entries (OF), distance travelled (OF), freezing (CFT) | 5             | Emotionality (Balazsfi et al., 2018)           |
|                                                      |                             | OF, EPM                       | Distance travelled during S min (OF), closed arm entries (EPM) | 2             | Locomotion                                     |
| Research Animal                                     | NA                          | mHB                           | Number of board entries (avoidance), latency until first board entry (avoidance), time on the board (avoidance) | 3             | Avoidance (Labots et al., 2018)                |
| Wellbeing & Methodology & Strain differences         |                             |                               | Number of stretched attend (risk assessment), latency until the first stretched attend (risk assessment) | 2             | Risk Assessment                                |
|                                                      |                             |                               | Number of self-grooming (arousal), latency until first self-grooming (arousal), time self-grooming (arousal), number of defecations (arousal), latency until first bolus (arousal) | 5             | Arousal                                        |
|                                                      |                             |                               | Z-avoidance, Z-risk assessment, Z-arousal | 10           | Anxiety                                        |
|                                                      |                             |                               | Number of being motionless (immobility), latency until the first time the mouse is motionless (immobility), time being motionless (immobility) | 3             | Immobility                                     |
|                                                      |                             |                               | Number of line crossings (locomotion), latency until first line crossing (locomotion), number of rearing in the box (locomotion), latency until the first rearing in the box (locomotion), number of readings on the board (locomotion), latency until the first rearing on the board (locomotion) | 6             | Locomotion                                     |
| Major depressive disorder and/ Anxiety               | No model                    | Zero, LD, TST, FST            | Z-locomotion, Z-immobility Time immobile (FST), time immobile (TST), open arm time (Zero), distance travelled in open (Zero), time in light side (LD), mean visit to light side (LD) | 9             | Activity (Lax et al., 2018)                    |
|                                                      |                             |                               |                                                   | 6             | Emotionality                                   |
| Gestational/ Development                             | No Model                    | Physical milestones, Reflex development | Weight, fur development, pinna detachment, eyes opening, superior incisor eruption, testis descending/ vaginal opening, palmar grasp reflex, righting reflex, free-fall righting, walking | 10            | Developmental                                  |
|                                                      |                             |                               |                                                   |               | (Motta-Teixeira et al., 2018)                  |
| Major depressive disorder and/ Anxiety               | Unpredictable chronic mild stress | EPM, OF                       | Time in the open arms (EPM), open arm entry ratio (EPM), | 4             | Anxiety (Page and Coutellier, 2018)            |
|                                                      |                             |                               |                                                   |               |                                                |

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| Area of research | Animal model paradigm | Behavioural tests | Behaviours integrated (Test) | Z-score /Index | Reference |
|------------------|-----------------------|------------------|-----------------------------|----------------|-----------|
| Major depressive disorder and/Anxiety | Chronic stress exposure | FST, TST | time in the centre (OF), thigmotaxis ratio (OF) | 5 Depression | (Pévrot et al., 2018) |
| Major depressive disorder and/Anxiety | T-Maze |  | Alterations (%) (T-maze), latency (T-maze) | 2 Working Memory | |
| Major depressive disorder and/Anxiety | EPM |  | Latency to enter open arms (EPM), entries into open arm (EPM), time in the open arm (EPM), time in the open arm (EPM) | 4 Anxiety | |
| Major depressive disorder and/Anxiety | Unpredictable chronic mild stress | Marbles, EPM, TST, FST | Marbles buried (Marbles), time spent on the open arm (EPM), open arm entries (EPM), immobility (TST), immobility (FST) | 5 Emotionality | (Sutton et al., 2018) |
| Major depressive disorder and/Anxiety | Peripubertal Stress protocol | RIT | Offensive behaviour duration (RIT), offensive behaviour frequency (RIT), latency to offend (RIT), frequency of bites with any abnormal component (RIT), proportion of all bites that were not signalled (RIT), targeted toward vulnerable body parts or excessively ‘hard’ (RIT) | 6 Aggression | (Walker et al., 2018) |
| Major depressive disorder and/Anxiety | Unpredictable chronic mild stress | EPM, OF, NSF, Cookie | Time spent in the open arms (EPM), entries in the open arms (EPM), time spent in centre (OF), distance travelled in the centre (OF), latency to eat a food pellet (NSF), time of first cookie consumption (Cookie) | 6 Emotionality | (Oh et al., 2019) |
| Major depressive disorder and/Anxiety | Psychedelic N, N-Dimethyltryptamine | EPM | Time spent in the open arms (EPM), time spent in closed arms (EPM), number of open arm entries (EPM), number of closed arm entries (EPM) | 4 EPM score | (Cameron et al., 2019) |
| Major depressive disorder and/Anxiety | NIL |  | Distance travelled (NIL), degree of thigmotaxis (NIL), number of rearing (NIL), time spent rearing (NIL) | 4 Locomotion | |
| Major depressive disorder and/Anxiety | Unpredictable chronic mild stress | Marbles, EPM, TST, FST | Number of marbles buried (Marbles), time spent on the open arm (EPM), number of entries into the open arm (EPM), immobility (TST), immobility (FST) | 5 Emotionality | (Orlandi et al., 2019) |
| Major depressive disorder and/Anxiety | perinatal exposure to selective serotonin reuptake inhibitor | OF, EPM | Distance moved (OF), time in the centre (OF), distance moved (EPM), per cent in the open arms (EPM) | 4 Anxiety | (Glover et al., 2019) |
| Major depressive disorder and/Anxiety | Gestational/Development high fat high sucrose maternal diet | OISB | Number of respiratory cycles/second (frequency), size of inspiration phases (amplitude) | 2 Sniffing index | (Merle et al., 2019) |
| Major depressive disorder and/Anxiety | Gestational/Development Exposure to early-life stress | OR, OL, MWM | Ratio novel/familiar (OR), ratio novel/familiar (OL), time to platform (MWM), time in target quadrant (MWM) | 4 Hippocampal Memory/Learning | (Yam et al., 2019) |
| Major depressive disorder and/Anxiety | Chronic non-discriminatory social defeat stress | LD, EPM, SPT, NSF | Time in the light (LD), distance in the light (LD), time on the open arms (EPM), distance on open arms (EPM), sucrose preference (SPT), latency to feed (NSF) | 6 Emotionality | (Yohn et al., 2019) |

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| Area of research                          | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score/Index | Reference                   |
|------------------------------------------|-----------------------|-------------------|-----------------------|---------------|-----------------------------|
| **Emotional regulation**                 | No Model              | mHB               | Number of board entries (avoidance), latency until first board entry (avoidance), time on the board (avoidance) | 3             | Avoidance                   |
|                                          |                       |                   | Number of risk assessments (risk assessment), latency until the first risk assessment (risk assessment) | 2             | Risk Assessment             |
|                                          |                       |                   | Number of self-grooming (arousal), latency until first self-grooming (arousal), time self-grooming (arousal), number of defecations (arousal), latency until first bolus (arousal) | 5             | Arousal                     |
|                                          |                       |                   | Number of rearing in the box (exploration), latency until first rearing in the box (exploration), number of rearing on the board (exploration), latency until first rearing on the board (exploration), number of hole explorations (exploration), latency until first hole exploration (exploration), number of hole visits (exploration), latency until first hole visit (exploration) | 8             | Exploration                 |
| **Postoperative delirium /cognitive dysfunction** | Tibial fracture operation | OF               | Time spent in the centre area (OF), distance moved in the centre area (OF) | 2             | Emotionality                |
|                                          |                       |                   | Recognition index of time (NOR), recognition index of distance (NOR), time spent freezing (FC), moving paths (MWM), time required for locating the hidden escape platform (MWM) | 5             | Hippocampal Memory/Learning |
| **Premenstrual dysphoric disorder**      | Genetic               | OF, ST            | Time in centre (OF), number of centre crossings (OF), time in corner (OF), time spent grooming (ST), number of grooming sessions (ST) | 5             | Emotionality                |
|                                          |                       |                   | Centre entries (OF), distance in the light chamber (LD), time in open arms (EPM) | 3             | Emotionality                |
|                                          |                       |                   | Distance travelled (LD), distance travelled in the boarder (OF) | 2             | Locomotion                  |
| **Emotional regulation**                 | Genetic               | OF, LD, EPM       | Time spent in the open arms /total time on the maze (EPM), number of entries to the open arms/total exploration on the maze (EPM) | 2             | Anxiety                     |
|                                          |                       |                   | Anogenital sniffing (SI), interfacial sniffing (SI), pursuit, (SI), active avoidance (SI) | 4             | Sociability                 |
| **Posttraumatic stress disorder**        | Predator-scent stress | EPM               | Coat state (Coat), latency time (NOR), number of crossed squares (NOR), quality score (Nest), sucrose consumption (SPT), immobility duration (TST), latency before the first grooming (ST), grooming duration (ST), time in open arm (EPM), visits to open arm (EPM) | 10            | Emotionality                |
| **Psychosis/Schizophrenia**              | acute NMDA receptor antagonist | SI               | Anogenital sniffing (SI), interfacial sniffing (SI), pursuit, (SI), active avoidance (SI) | 4             | Sociability                 |
| **Major depressive disorder and/Anxiety**| Unpredictable chronic mild stress | Coat, NOR, Nest, SPT, TST, ST, EPM | Coat state (Coat), latency time (NOR), number of crossed squares (NOR), quality score (Nest), sucrose consumption (SPT), immobility duration (TST), latency before the first grooming (ST), grooming duration (ST), time in open arm (EPM), visits to open arm (EPM) | 10            | Emotionality                |
| Area of research                          | Animal model paradigm                                      | Behavioural tests                          | Behaviours integrated                                        | Z-score /Index | Reference                               |
|------------------------------------------|------------------------------------------------------------|--------------------------------------------|---------------------------------------------------------------|----------------|-----------------------------------------|
| Major depressive disorder and/ Anxiety  | Social isolation                                           | FST, OF, NSF, LD, SPT, EPM                | Distance travelled (OF), relative position within the arena (OF), time spent actively swimming (FST), passively floating (FST), time spent in the light compartment (LD), latency to feeding (NSF), sucrose consumption (SPT), time spent in the open arms (EPM), time in the closed arm (EPM) | 6              | Emotionality (Oliver et al., 2020)     |
| Major depressive disorder and/ Anxiety  | Corticosterone and social defeat                            | SPT, SI, Zero, OF, Coat                   | Sucrose intake (SPT), interaction time (SI), time in open zone (Zero), latency to enter open zone (Zero), exploration time (OF), coat state score (Coat) | 5              | Depression (Orrico-Sanchez et al., 2020) |
| Major depressive disorder and/ Anxiety  | Chemical lesioning of the ventral subiculum                | OF, EPM, SI                               | Time spent in the centre (OF), distance in periphery/total distance ratio (OF), time in the open arms (EPM), open/closed arms entries ratio (EPM), social preference index (SI), social novelty index (SI) | 3              | Anxiety (Subhadeep et al., 2020)       |
| Major depressive disorder and/ Anxiety  | Chronic retrain stress                                     | SI, FST                                   | Social avoidance (SI), immobility time (FST)                   | 2              | Complementary/ Composite/ Cumulative behavioural Emotionality (Cherix et al., 2020) |
| Major depressive disorder and/ Anxiety  | No model                                                   | EPM, LD                                   | Head dipping (EPM), exit attempts (LD)                         | 2              | Emotionality (Daugj et al., 2020)      |
| Major depressive disorder and/ Anxiety  | Maternal deprivation                                       | OF                                        | Visits to the central area (OF), rearing (OF)                 | 1              | Emotionality (Fazekas et al., 2020)    |
| Posttraumatic stress disorder            | Trauma (induced by electric foot shocks)                  | CF, SI, EPM                               | Freezing (CF), distance travelled (SI), velocity (SI), frequencies to enter into the central area (SI), distance travelled (EPM), open arm frequencies (EPM), closed arm frequencies (EPM) | 3              | Anxiety (Meyer et al., 2020)           |
| Research Animal Wellbeing & Methodology & Strain differences | three different blood sampling techniques or two control treatments | OF, NOR SI                                | Distance travelled (OF), distance travelled (NOR), distance travelled (SI) | 3              | Locomotion (Meyer et al., 2020)        |
| Research Animal Wellbeing & Methodology & Strain differences | Aged                                                       | OF                                        | Distance moved in 10 min (OF), maximal distance moved between bouts of inactivity (OF), duration of travel (OF), time spent walking (OF), change in direction per unit distance travelled (OF), velocity of movement over 10 min (OF), rearing frequency (OF) | 1              | Locomotion (Ilerrera et al., 2020)    |
| Research Animal Wellbeing & Methodology & Strain differences | Social isolation                                           | Burrow                                    | Burrowed material values of each training and testing day (Burrow) | 1              | Emotionality (Begni et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | OF                                                         | Velocity (OF), distance moved (OF), movement values (OF) | Number of faeces (OF), number of rearing (OF), time spent in the centre (OF), ‘distance to walls’ (OF) | 3              | Emotionality (Begni et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | Chronic retrain stress                                     | SI, FST                                   | Social avoidance (SI), immobility time (FST)                   | 2              | Complementary/ Composite/ Cumulative behavioural Emotionality (Cherix et al., 2020) |
| Research Animal Wellbeing & Methodology & Strain differences | No model                                                   | EPM, LD                                   | Head dipping (EPM), exit attempts (LD)                         | 2              | Emotionality (Daugj et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | Maternal deprivation                                       | OF                                        | Visits to the central area (OF), rearing (OF)                 | 1              | Emotionality (Fazekas et al., 2020)    |
| Research Animal Wellbeing & Methodology & Strain differences | Trauma (induced by electric foot shocks)                  | CF, SI, EPM                               | Freezing (CF), distance travelled (SI), velocity (SI), frequencies to enter into the central area (SI), distance travelled (EPM), open arm frequencies (EPM), closed arm frequencies (EPM) | 3              | Anxiety (Meyer et al., 2020)           |
| Research Animal Wellbeing & Methodology & Strain differences | three different blood sampling techniques or two control treatments | OF, NOR SI                                | Distance travelled (OF), distance travelled (NOR), distance travelled (SI) | 3              | Locomotion (Meyer et al., 2020)        |
| Research Animal Wellbeing & Methodology & Strain differences | Aged                                                       | OF                                        | Distance moved in 10 min (OF), maximal distance moved between bouts of inactivity (OF), duration of travel (OF), time spent walking (OF), change in direction per unit distance travelled (OF), velocity of movement over 10 min (OF), rearing frequency (OF) | 1              | Locomotion (Ilerrera et al., 2020)    |
| Research Animal Wellbeing & Methodology & Strain differences | Social isolation                                           | Burrow                                    | Burrowed material values of each training and testing day (Burrow) | 1              | Emotionality (Begni et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | OF                                                         | Velocity (OF), distance moved (OF), movement values (OF) | Number of faeces (OF), number of rearing (OF), time spent in the centre (OF), ‘distance to walls’ (OF) | 3              | Emotionality (Begni et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | Chronic retrain stress                                     | SI, FST                                   | Social avoidance (SI), immobility time (FST)                   | 2              | Complementary/ Composite/ Cumulative behavioural Emotionality (Cherix et al., 2020) |
| Research Animal Wellbeing & Methodology & Strain differences | No model                                                   | EPM, LD                                   | Head dipping (EPM), exit attempts (LD)                         | 2              | Emotionality (Daugj et al., 2020)      |
| Research Animal Wellbeing & Methodology & Strain differences | Maternal deprivation                                       | OF                                        | Visits to the central area (OF), rearing (OF)                 | 1              | Emotionality (Fazekas et al., 2020)    |
| Research Animal Wellbeing & Methodology & Strain differences | Trauma (induced by electric foot shocks)                  | CF, SI, EPM                               | Freezing (CF), distance travelled (SI), velocity (SI), frequencies to enter into the central area (SI), distance travelled (EPM), open arm frequencies (EPM), closed arm frequencies (EPM) | 3              | Anxiety (Meyer et al., 2020)           |
| Area of research | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score/Index | Reference |
|------------------|------------------------|-------------------|-----------------------|---------------|-----------|
| **Major depressive disorder and/ or Anxiety** | Olfactory bulbs removal | OF, EPM, LD | (SI), number of entries to the interaction zone (SI), time spent in the outer zone (SI) | 7 | Emotionality (Nedogreeva et al., 2020) |
| **Major depressive disorder and/ or Anxiety** | Chronic multimodal restraint stress | SI, FST, SPT | Proportion of thigmotaxis (OF), number of faecal boluses (OF), time spent in the open arms (EPM), open arms entries (EPM), numbers of peeps (LD), visits to the open space (LD), number of faecal boluses (LD) | 3 | No characterisation (Weger et al., 2020) |
| **Major depressive disorder and/ or Anxiety** | Unpredictable chronic mild stress | Coat, ST, SPT, FST | Social avoidance (SI), time of immobility (FST), sucrose preference (SPT), immobility time (FST) | 4 | Emotionality (Cardinal et al., 2021) |
| **Major depressive disorder and/ or Anxiety** | Chronic restraint stress | Coat, SPT, PhenoTyper | Coat state score (Coat), sucrose preference (SPT), time spent in the shelter (PhenoTyper) | 3 | Emotionality (Codeluppi et al., 2021) |
| **Major depressive disorder and/ or Anxiety** | low-dose bilateral intracerebroventricular infusion of PHP.eB serotype | PhenoTyper, EPM, OF, NSF, NIH | Shelter zone area under the curve (PhenoTyper), time spent in open arms (EPM), time spent in the inner zone (OF), latency to feed (NSF), latency to drink milk (NIH) | 5 | Anxiety (Fee et al., 2021) |
| **Stress** | Limited cheese intake | NOR, Restraint, SI, EPM | Number of object interactions (NOR), time spent in object interactions (NOR), number of struggling events (Restraint), time spent struggling (Restraint), number of social chamber visits (SI), duration of social chamber visits (SI), number and duration of sniffing bouts (SI), social preference (SI), number and duration of open arm visits (EPM), duration of head dipping behaviour (EPM) | 10 | Global performance/Total (Fourman et al., 2021) |
| **Major depressive disorder and/ or Anxiety** | miR-323-3p was overexpressed or knocked-down | OF, EPM, TST | Time spent in the corners (OF), time spent in centre (OF), distance travelled (OF), time spent in closed arm (EPM), time spent in open arm (EPM), time spent in centre (EPM), relative mobility time (TST) | 7 | Emotionality (Fiori et al., 2021) |
| **Gut Microbiome** | Antibiotic Treatment | OF, EPM | Time in open arms (EPM), immobility times (FST), latency to feed (NSF) | 3 | Negative Affect (Gergues et al., 2021) |
| **Gut Microbiome** | Chronic corticosterone / Social defeat stress | EPM, NSF, FST | Time in open arms (EPM), immobility times (FST), latency to feed (NSF) | 6 | Anxiety (Glover et al., 2021) |
| **Gut Microbiome** | Antibiotic Treatment | OF, EPM | Centre time (OF), time in open arms (EPM), locomotor activity (OF), locomotor activity (EPM), faecal bolus (OF), faecal bolus (EPM) | 5 | Coping |

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| Area of research         | Animal model paradigm                                         | Behavioural tests               | Behaviours integrated                                                                 | Z-score/Index | Reference                          |
|--------------------------|----------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------|---------------|------------------------------------|
| Major depressive disorder and Anxiety | Retrovirus-based loss-of-function approach OF, Cylinder, EPM (Week 4 and Week 10) | 3 Time spent in the centre (OF), distance ratio (OF), latency to emerge from the cylinder (Cylinder), number of re-entries in the cylinder (Cylinder), Time spent in open arms (EPM *2), ratio between entries in open arms divided by entries in closed and open arms (EPM*2) | 8 Anxiety     | (Kerloch et al., 2021)            |
|                          |                                                                  | SPT, FST                        | 2 Sucrose preference ratio (SPT), latency to immobility (FST), immobility time in the last 4 min of the test (FST) | 3 Depression  |                                    |
| Gestational/Development  | Prenatal stress NSF, SPT, SI, OF | 4 Latency to eat (NSF), sucrose preference (SPT), social investigation ratio (SI), distance travelled (OF), number of entries in the periphery (OF), time spent in the periphery (OF), number of entries in the centre (OF), time spent in the centre (OF), latency to enter the centre (OF) | 9 Complementary/ Composite/ Cumulative behavioural | (Marchisella et al., 2021) |
| Major depressive disorder and Anxiety | Chronic corticosterone / Social defeat stress LD, ST | 2 Latency to dark (LD), latency to light (LD), grooming time (ST), number of grooming sessions (ST), grooming latency (ST) | 5 Complementary/ Composite/ Cumulative behavioural | (Marrocco et al., 2021) |
| Major depressive disorder and Anxiety | Chronic restraint stress Coat, PhenoTyper, SPT, NSF | 4 Coat state score (Coat), sucrose preference (SPT), time spent in the shelter (PhenoTyper), latency to bite (NSF) | 4 Emotionality | (Misquitta et al., 2021a) |
| Major depressive disorder and Anxiety | Chronic restraint stress PhenoTyper, SPT, NSF | 3 Residual avoidance (PhenoTyper), sucrose consumption (SPT), latency to bite (NSF) | 3 Emotionality | (Misquitta et al., 2021b) |
| Major depressive disorder and Anxiety | Chronic mild stress SPT, EPM | 2 Sucrose consumption (SPT), time in the open arms (EPM), number of entries in the open arms (EPM) | 3 Emotionality | (Paladini et al., 2021) |
| Hypoxic ischemic brain injury | Neonatal hypoxic ischemic encephalopathy-Surgery Geotaxis, NOR Cylinder | 3 Discrimination index at PND30 (NOR), discrimination index at PND50 (NOR), right foot touches at PND30 (Cylinder), right foot touches at PND50 (Cylinder), time to turn (Geotaxis), time to cross (Geotaxis) | 6 Behavioural burden | (Penny et al., 2021b) |
| Hypoxic ischemic brain injury | Neonatal hypoxic ischemic encephalopathy-Surgery Geotaxis, NOR Cylinder | 3 Discrimination index at PND30 (NOR), discrimination index at PND50 (NOR), right foot touches at PND30 (Cylinder), right foot touches at PND50 (Cylinder), time to turn (Geotaxis), time to cross (Geotaxis) | 6 Complementary/ Composite/ Cumulative behavioural | (Penny et al., 2021a) |
| Obesity genetic | Early suckling behaviour, Food intake, Liquid taste preference, Food motivation, Detailed 24 h meal pattern, Behavioural Satiety Sequence | 6 Weight gain (Early suckling behaviour), Daily food intake SD (Food intake), Daily food intake HDF (Food intake), sweet taste intake (Liquid taste preference), fat taste intake (Liquid taste preference), ingestion score (Food motivation), inverse of distraction number during the first walk to the Goal Box (Food motivation), meal number during night phase (Detailed 24 h meal pattern), food intake/meal during night | 11 Integrative calculated behavioural | (Pocheron et al., 2021) |

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| Area of research                           | Animal model paradigm            | Behavioural tests | Behaviour tests | Behaviours integrated                      | Z-score/Index | Reference                      |
|-------------------------------------------|----------------------------------|-------------------|-----------------|---------------------------------------------|---------------|---------------------------------|
| Cognition/ Cognitve Decline               | Aged                             | MWM               | 1               | Swimming distance (MWM), time spent in each quadrant (MWM), discrimination index (MWM), number of annulus crossings (MWM) | 4             | Global performance/Total        | (Rizzolo et al., 2021) |
| Posttraumatic stress disorder Research Animal Wellbeing & Methodology & Strain differences | Arousal-based individual screening no model | PPI               | 1               | Repeated acoustic startle reactivities (PPI) | Arousal       | (Torrisi et al., 2021)          |
|                                           |                                   | mHB               | 1               | Board entries (avoidance), latency until first board entry (avoidance), time on the board (avoidance) | 3             | Avoidance                      | (van der Goot et al., 2021) |
|                                           |                                   |                   |                 | Number of risk assessments (risk assessment), latency until the first risk assessment (risk assessment) | 2             | Risk Assessment                 |
|                                           |                                   |                   |                 | Number of self-grooming (arousal), latency until first self-grooming (arousal), time self-grooming (arousal), number of defecations (arousal), latency until first bolus (arousal) | 5             | Arousal                         |
|                                           |                                   |                   |                 | Number of rearing in the box (exploration), latency until first rearing in the box (exploration), number of rearing on the board (exploration), latency until first rearing on the board (exploration), number of hole explorations (exploration), latency until first hole exploration (exploration), number of hole visits (exploration), Latency until first hole visit (exploration) | 8             | Exploration                     |
|                                           |                                   |                   |                 | Number of line crossings (locomotion), Latency until first line crossing (locomotion) | 2             | Locomotion                      |
| Major depressive disorder and Anxiety     | Unpredictable chronic mild stress / learned helplessness | EPM, OF, NSF, NIH | 4               | Latency to feed (NSF), cumulative immobility (TST), sucrose preference (SPT), latency to drink the reward (NIH), time spent in open arms (EPM), time spent in closed arms (EPM), open arm entries (EPM), closed arms entries (EPM) | 10            | Anxiety                         | (Bansal et al., 2022) |
|                                           |                                   |                   |                 | Sucrose consumption (SPT), latency to drink the reward (NIH) | 2             | Anhedonia                       |
|                                           |                                   |                   |                 | Latency to feed (NSF), cumulative immobility (TST), sucrose preference (SPT), latency to drink the reward (NIH), time spent in open arms (EPM), time spent in closed arms (EPM), open arm entries (EPM), closed arms entries (EPM), sucrose consumption (SPT), Coat score (Coat) | 12            | Emotionality                    |
| Major depressive disorder and Anxiety     | Chronic restraint stress / Unpredictable Chronic Mild Stress | EPM, NSF, PhenoTyper, Coat, FST, SPT | 6               | Time spent in open arms (EPM), open arm entries (EPM), Latency to approach | 9             | Emotionality                    | (Bernardo et al., 2022) |
| Area of research | Animal model paradigm | Behavioural tests | Behaviours integrated | Z-score /Index | Reference |
|------------------|-----------------------|-------------------|----------------------|---------------|-----------|
|                  |                       | **Tests**         | **Count**            | **Behaviours (Test)** | **Count** |
| Major depressive disorder and Anxiety | HFD for 6 weeks | EPM, LD | 2 | Time spent in the centre (EPM), time spent in the dark (LD), centre time/distance moved ratio (OF) | 3 | Anxiety | (Bullich et al., 2022) |
|                  |                       | SI, TST, FST | 3 | Time interacting with the familiar mouse (SI), time of immobility (FST), time of immobility (TST) | 3 | Depression | |
| Major depressive disorder and Anxiety | Corticosterone | LD, ST | 2 | Time in the light (LD), latency to dark (LD), latency to light (LD), grooming time (ST), number of grooming sessions (ST), grooming latency (ST) | 6 | Complementary/ Composite/ Cumulative behavioural | (Caradonna et al., 2022a) |
| Major depressive disorder and Anxiety | Corticosterone / Chronic social defeat stress | LD, ST | 2 | Time in the light (LD), latency to dark (LD), latency to light (LD), grooming time (ST), number of grooming sessions (ST), grooming latency (ST) | 6 | Complementary/ Composite/ Cumulative behavioural | (Caradonna et al., 2022b) |
| Substance use disorders | no model | NA | 0 | Naloxone-induced jumping, rearing (number of events), forepaw tremors (number of shakes unrelated to grooming), wet dog shakes (full body shakes unrelated to grooming), forepaw licking (number of non-grooming licking bouts) | 5 | Withdrawal severity | (Lewter et al., 2022) |
| Major depressive disorder and Anxiety | Unpredictable chronic mild stress | Coat, PhenoTyper, OF, EPM, NIH, SPT, NSF, FST | 8 | Coat state (coat), time shelter zone duration (PhenoTyper), centre time during the first 5 min of tests (OF), time in open-arm (EPM), frequency of entry into open arm (EPM), latency to feed (NIH), rate of sucrose consumption (SPT), latency to feed (NSF), immobility time (FST) | 9 | Emotionality | (Tomoda et al., 2022) |
| Pain | Multiple virus, intercranial and surgery | OF, EPM, LD | 3 | Time spent in the centre zone (OF), time spent in the open arms (EPM), time spent in the light side (LD) | 3 | Emotionality | (Yamasuchi et al., 2022) |
| Major depressive disorder and Anxiety | Chronic variable stress | NSF, ST, FST, EPM, SPT | 5 | Latency to eat (NSF), time spent grooming (ST), latency to immobility (FST), time spent in open arms (EPM), sucrose preference (SPT) | 5 | Emotionality | (Bittar et al., 2021) |
| Alzheimer’s disease | genetic | EPM, OF | 2 | Open arm time (EPM), peripheral distance during the first 10 min (OF) | 2 | Emotionality | (Arandelović et al., 2021) |
|                  |                       | Beam | 1 | Duration of slips (Beam), number of slips (Beam) | 2 | Motor | |
|                  |                       | EPM, OF | 2 | Closed arm entries (EPM), distance during the last 5 min (OF) | 2 | Motivation | |
| Pregnancy food cravings | “Limited access” paradigm | OF, LD, EPM | 3 | Time in centre (OF), time spent in light (LD), time in open arm (EPM) | 3 | Anxiety | (Iljadad-Tovoli et al., 2022) |
| Substance use disorders | viral-mediated disruption of molecular clock function | OF, LD, EPM, NSF | 4 | Centre entries (OF), time in light (LD), time open arm (EPM), latency to eat (NSF) | 4 | Exploration | (Becker-Krall et al., 2022) |
| Olfaction | Dietary intervention | OISB | 1 | Number of respiratory cycles/ second (frequency), size of inspiration phases (amplitude) | 2 | Sniffing index | (Soubreyre et al., 2022) |

Note: open field test (OF), elevated plus maze test (EPM), light dark box test (LD), modified hole board test (mHB), social interaction test (SI), tail suspension test (TST), forced swim test (FST), novelty suppression of feeding (NSF), sucrose preference test (SPT), splash test (ST), cookie test (Cookie), fear conditioning test (FC), Working memory test (WM), Morris Water Maze (MWM), novel object recognition test (NOR), Beam walk test (Beam), visible platform water maze (VPWM), maternal behaviours (Maternal), Nest building test (Nest), Puzzle box (Puzzle), attentional set shifting task (ASST), Acoustic Startle Response (ASR), Resident Intruder test (RIT),
mentioned techniques were used to calculate the integrated behavioural z-score. Justification should be provided for integrating behaviours.

Although combining complementary data might create stronger evidence, this will result in potentially overlooking important individual results and reduce comparability across studies. Integrated behavioural z-scoring allows for combining and comparing them to the absolute controls of that study. Integrated behavioural z-scores can be compared across studies even if individual result might show conflicting results. Studies presented here used different behaviours and behavioural test to measure the same construct in mice. In future, studies should aim to use the same or comparable behaviours to create consistency and reproducibility between laboratories when measuring specific constructs.

Reporting individual results allows for comparing results across studies. All publications reviewed here still report all individual results and use the integrated behavioural score as an additional variable to improve predictive validity by combining converging evidence.

Researchers using behavioural z-scoring will need to take care to not over-value individual behaviours in comparison to the condition in humans. Using behavioural z-scoring authors can determine, how much weight they give each individual behaviour parameter, which could result in creating an imbalanced representation of the results. This can be negative, if not presented transparently, however, on the contrary, being able to place greater importance on a specific variable might help to closer resemble the human disease phenotype and with this improve construct validity. Here, it will be important for the author to provide a transparent description and justification of the weight place on individual behaviour/biological variables.

Creating one score improves non-topic experts to interpret and understand behavioural data. This could allow for easier comparison of behaviours with biological variables. Authors should aim to model the integrated behavioural z-score on the human complex psychological and physiological condition (Wittchen et al., 2014). The current emotional behavioural z-score solely relies on behavioural measures ignoring the biological changes. Below in future perspective uses of z-scoring, I describe the possibility of creating a comprehensive disease-specific z-score (Fig. 5), which uses behavioural and biological variables to create converging evidence.

4.4. Future use of integrated behavioural z-scores

Integrated behavioural z-score has mostly been used in the field of anxiety and major depressive disorder to assess emotionality in animal models (Fig. 3, Table 1). Within the following section, I will be proposing further potential ideas to use an integrated behavioural z-score beyond its original proposed purpose. I would like to propose to investigate behavioural domains, such as social, anxiety-like, depressive-like and cognitive behaviour to create disease related z-scores comparable to humans currently used. Current z-score literature has started to investigate specific behavioural domains such as “Depression-like z-score” (Apazoglou et al., 2018; Bullich et al., 2022; de Sá-Caçada et al., 2015; Glover et al., 2019; Huynh et al., 2011; Kerloch et al., 2021; Orrico-Sanchez et al., 2020; Subhadeep et al., 2020), “Anhedonia z-score” (Bansal et al., 2022; Fee et al., 2021) and “Social z-score” (Giacomin et al., 2018; Glover et al., 2019). Currently, there is a lack for consistency of how many and which behaviours and behavioural test are to be integrated into an integrated behavioural z-score (Table 1). Inconsistency between studies will reduce comparability between studies. Creating behavioural domains might improve consistency. Here, I am proposing behavioural domains relevant for schizophrenia.

Individuals with schizophrenia are currently assessed according to the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Patients are rated from 1 to 7 in 30 different symptom scales differentiated into the positive, negative, and general psychopathology scale (Kay et al., 1987; Leucht et al., 2005). Animal behavioural test can also be classified into these three domains (Fig. 4, this list is only an example and is not exhaustive). We can generate an individual z-score per behavioural domain as performed for humans. After generating an integrated z-score for each individual domain an overall schizophrenia-like behaviour integrated z-score could be generated. 1.

Step 1. Generate z-score for each individual test.

\[
z = \frac{X - \mu}{\sigma}
\]

Step 2. Cluster conceptually related behaviours together as suggested in Fig. 4 into behavioural domains.

Overall Positive scale Integrated behavioural z-score

\[
\text{Overall Positive scale Integrated behavioural z-score} = \frac{Z_{test1} + Z_{test2} + Z_{test3} + \ldots}{\text{Number of Tests}}
\]

Overall Negative scale Integrated behavioural z-score

\[
\text{Overall Negative scale Integrated behavioural z-score} = \frac{Z_{test1} + Z_{test2} + Z_{test3} + \ldots}{\text{Number of Tests}}
\]

Fig. 4. Murine behavioural test relating to the criteria of the Positive and Negative Syndrome Scale (PANSS).
Step 3. All three scales are combined into one overall schizophrenia-like behaviour integrated z-score.

\[
Z_{\text{Overall Schizophrenia}} = Z_{\text{Positive scale}} + Z_{\text{Negative scale}} + Z_{\text{General Psychopathology scale}} + \ldots
\]

\[
\text{Integrated behavioural } Z = \frac{Z_{\text{Physiological integrated z-core}} + Z_{\text{Psychological integrated z-core}} + Z_{\text{Overall General Psychopathology scale integrated behavioural z-score}} + \ldots}{\text{Number of Tests}}
\]

The benefits of a stepwise approach would allow for transparency of individual behavioural results influencing the integrated scores. Investigating individual domains can demonstrate if treatment options might be more beneficial for one domain compared to another. Lastly, using the overall schizophrenia-like behaviour integrated z-score would create one objective measure, like the PANSS in humans. This objective measure might be used to determine how effective potential novel therapeutic treatment options might be. Beyond, the benefits in the drug development process current and future animal models can be assessed for their translatability using the overall schizophrenia-like behaviour integrated z-score. This methodology could be applied to other neurodegenerative and neurodevelopmental disorders generating further disease specific integrated behavioural z-scores such as an Alzheimer’s disease score.

Overall, I suggest constructing overall disease specific integrated behavioural z-scores as proposed here for schizophrenia based on currently used diagnostic scales to increase face and predictive validity and with this translatability of animal research.

Neurodegenerative and neurodevelopmental disorders are a complex combination of psychological and physiological changes (Wittchen et al., 2014). Therefore, to understand the more complex pathophysiology, future research could use the same mathematical technique suggested here to generate a biological z-score, which could be further subdivided into various biological domains such as metabolic z-score (Zemdegs et al., 2016b), gene expression changes (Kerman et al., 2012) (Marchisella et al., 2020), antioxidant activation (Spero et al., 2022) or further parameters such as plasma corticosterone levels, hippocampal volume, electrophysiological recordings. These additional variables could be used to correlate physiological marker with psychological marker to understand potential relationships between variables. In addition, physiological and psychological marker could be integrated to produce a disease comprehensive score (Fig. 5). All approaches proposed would allow for greater understanding of complex psychiatric disorders increasing translatability between animal models to the human conditions, which is an interplay between behavioural and biological variability. This comprehensive approach would create converging evidence to not only minimise disorders to either a psychological condition or physiological condition but to create a whole-body approach increasing the predict validity of findings.

Additional application in animal research might include to use behavioural z-scoring in a repeated measure longitudinal study design to evaluate behavioural noise by investigating the individual behavioural trajectory of each mouse according to different experimental conditions sex and age (Bailey et al., 2006; Balcombe, 2006; Bohlen et al., 2014; Georgiou et al., 2022; Roedel et al., 2006; Shoji et al., 2016).

Other potential future applications of behavioural z-scoring might be applicable to human studies as it has been done for cognitive task in schizophrenia patients (Andrade, 2021) or potentially integrating demographic variables to be correlated with variables of interest. For instance, creating a socio-economic status index, this construct is complex and often measured using multiple measures such as education, income, and occupation (Anon, 2022). A socio-economic status index would allow to form a comprehensive view of the socio-economic status of a participant, which could be used to to understand the impact socio-economic status might have on the outcome variables.

5. Conclusion

In conclusion, within this perspective review, I set out to summarise the current uses and methodologies of integrated z-scoring. I found that integrated behavioural z-scoring has not yet been widely used within the broader literature but is a methodology of increasing interest. Here, I proposed to expand the use of this technique in other areas of behavioural neuroscience in neurodegenerative and neurodevelopmental disorders such as schizophrenia using an overall disease specific integrated behavioural z-scores based on currently used diagnostic scales, creating disease specific diagnostic domains. Domains will enable greater translatability of animal models by improving face and predict validity in areas such as the treatment development process. Additional application might include integrated socioeconomic status indexes in human studies. Integrated behavioural z-scoring provides strong support for disease- and treatment-related phenotypes.

Lastly, I proposed a comprehensive disease specific integrated z-score integrating behavioural pathology and pathophysiology increasing the predict validity of findings by create converging evidence to create a whole-body approach.

CRedit authorship contribution statement

The author (Ann-Katrin Kraeuter) is responsible for the conceptualisation of the researched idea within the manuscript, literature search and inclusion and writing of all drafts, revisions and editing of the final manuscript.

Conflict of Interest

The author has no competing interests to declare.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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