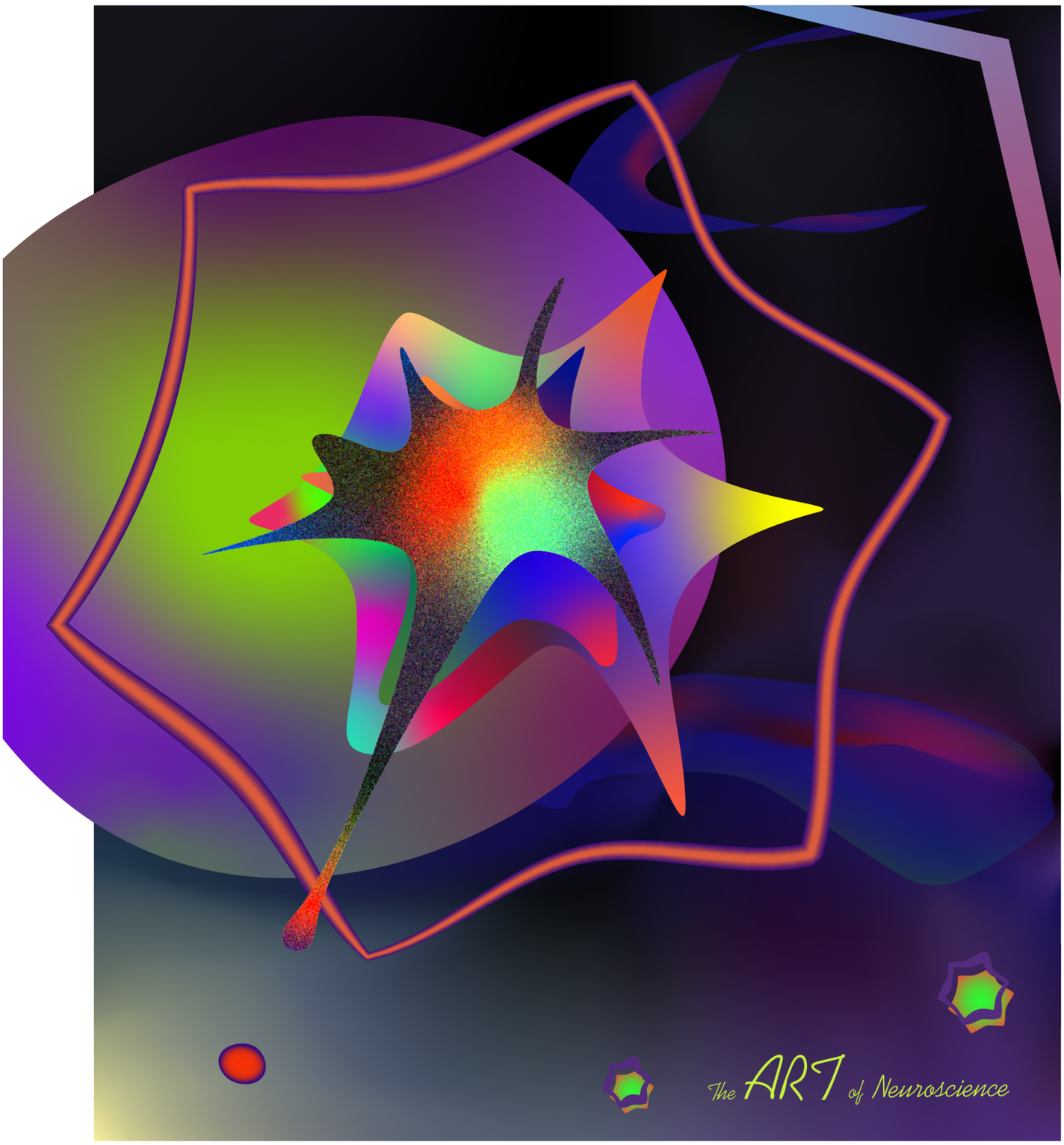
ABC Journal

AMSTERDAM BRAIN & COGNITION



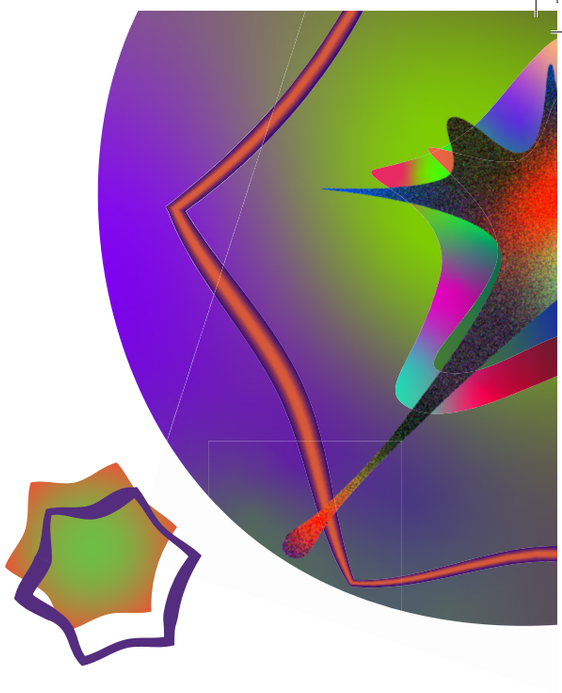
Issue 11. February, 2021

Art and Neuroscience
Suzanne Dikker: At the intersection between Art and Neuroscience

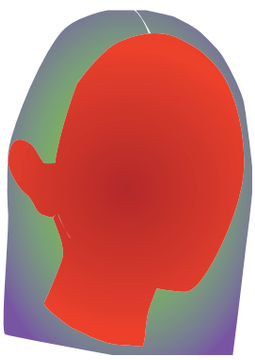
Neuraesthetics
Grounded in Science or merly satisfying?

Neuroscience & Proust
Opening doors for cross-discipline communication

ABC Journal
At the Intersection of Art and Neuroscience



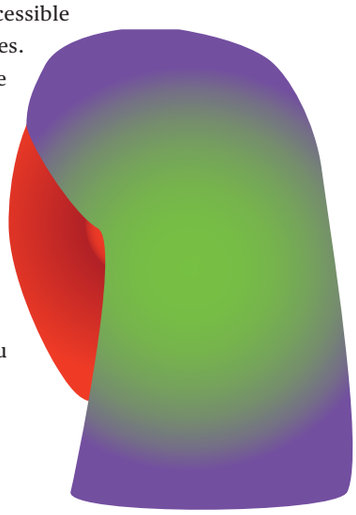
Issue 11 | January 2021



Editorial

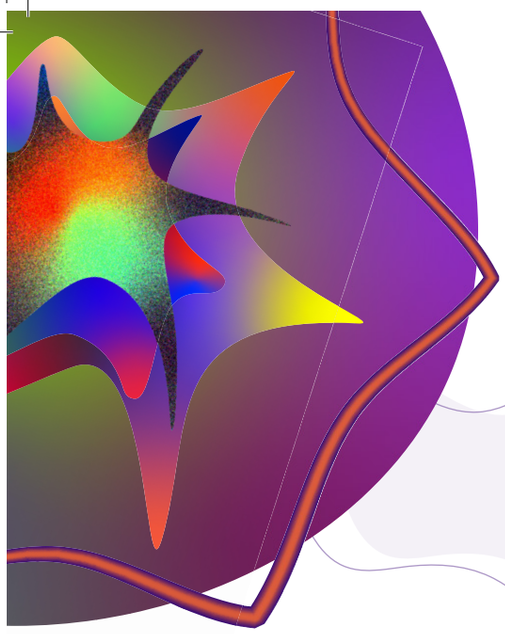
Six months have passed since we published our last issue, and as the global state of the world itself has been changed by the pandemic, our commitment to scientific communication has remained strong. Interestingly, with the new academic year, the ABC Journal also welcomed its new members to the cohort. And for the first time in this Journal's history, we created this issue without a single 'in-real-life' meeting. While this brought challenges, it also fueled creativity and unexpected companionship. And now, it's with this energy, we once again proudly present to you the 11th edition of the ABC Journal.

This issue places the theme of Art and Neuroscience, and how these concepts mutually relate to and feed into neuroscience at its core. Starting this issue, Lena, Michelle, and Lucia conduct an interview with Suzanne Dikker. The work of the latter stands at that sweet interdisciplinary spot, at the intersection between Art and Neuroscience, providing us renewed ways of looking into human behaviour. In another article, Marta raises critical questions such as 'what is the cognitive definition of beauty' or 'can our appreciation of the world's wonders be understood in terms of neural activations'. Continuing this foray, Ada and Rebecca write a review on Jonah Lehrer's Proust was a Neuroscientist, an easily accessible interdisciplinary book on the relationship between the creative and scientific disciplines. Finally, the newly founded Open Science Initiative at MBCS, drawing inspirations from the tenets of Open Science and its necessity for 'good research', propose four critical motivations aimed at young inspiring scientists that can lead to a more reliable, valid, generalisable, and approachable behavioural sciences.



Beyond the aforementioned featured articles, the heart of this journal yet again consists of original research projects made possible with the hard work of previously graduated MBCS students. Excitingly, for the first time in the Journals' history, we have also included literature reviews produced by our graduates. We hope that you raise multiple questions and find various answers concerning the fundamental link between Art and Neuroscience as you read through this issue.

Stay safe and – most importantly – stay safe,
Franck, Mubashir, and the ABC crew



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At the Intersection of Art and Neuroscience

"What the intersection of art and neuroscience has to offer and why naiveté can be the foundation of innovative neuroscience?" Through an interview with suzanne Dikker, we explore the fascinating relationship between the domains of Art and Neuroscience

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Use of prosody to mark information structure in autistic female and male adults with high-level language ability.

Nina Parrella - Prosody is a language domain involving stress, intonation and pitch. It typically assists in conveying meaning and emotion. In this research project, Nina investigate its use to mark information structure in autistic female and male adults with high-level language ability.

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Neuroaesthetics: Grounded in Science or Merely Aesthetically Pleasing?

This piece explores the research of beauty through the lens of mathematical equations, giving us insight into how the brain lights up when we see a beautiful piece of art.

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Psychedelics and the predictive mind

Evan Lewis-Healy - Evan reviews the research behind psychadelics (particularly, psilocybin) and the Preditive Processing theory, providing a possible mechanism for how psilocybin-assisted therapy may aid in treating major depressive disorders.

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Painting Hypotheses, Cooking Methods, and Composing Results Project

Here the authors discuss the book "Proust was a Neuroscientist" by Jonah Lehrer, which connects findings in artistic pieces that predate findings in neuroscience and psychology opening the door for communication across unrelated disciplines.

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Time Distortions

Nutsa Nanuashvili - In this piece, Nutsa provides us a review on the distortion of time in a clinical context. These distortions are a part of Alice in Wonderland syndrome, both of which little is understood.

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Better Research Practices: Own Your Research Decisions

The authors tackle an important subject: open science. In a time where science is plagued with unreplicable findings and lack of generalizability, the authors discuss 4 motivations for good/open research practices, while also providing us resources to get started.

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Dissociating contributions of periodic and aperiodic neural activity in human visual working memory.

Oscillatory activity and it's contributions to working memory changes is supported by ample evidence. However, Quirine re-examines data from a working task to disentangle the contributions of oscillatory and non-oscialltory activity in order to highlight the possible misinterpretations of neural activity changes.

At the Intersection of Art and Neuroscience

Lena Adel
Michelle Kühn
Lucia Liu

An interview with **Suzanne Dikker**

Suzanne Dikker works as a research scientist at the Max Planck Center for Language, Music and Emotion (CLaME) at New York University and the Emotion Regulation Lab at the Vrije Universiteit Amsterdam. She is also part of the art-science collective OOSTRIK + DIKKER and founder of MindHive, a platform that supports human brain and behavior research through community-based initiatives and student-teacher-scientist collaborations.

Dikker's research interest mainly revolves around the brain basis of dynamic human social interaction. Her work focuses on the prolific intersection of cognitive neuroscience, performance art and education. She promotes citizen science by employing the 'crowdsourcing' neuroscience technique. This out-of-the-lab experimental methodology allows simultaneously carrying out both lab and field research by applying scientifically controlled conditions in naturalistic human interactions. Dikker's projects consist of setting up installations in museums and at festivals by implementing Brain-Computer Interface (BCI) technology. She and her team explore 'human connectedness' by probing the behavioral responses and brain-to-brain coupling of social interactions.

For our current issue of the ABC journal, we met her online to talk about her work, what the intersection of art and neuroscience has to offer and why naiveté can be the foundation of innovative neuroscience.

Suzanne Dikker

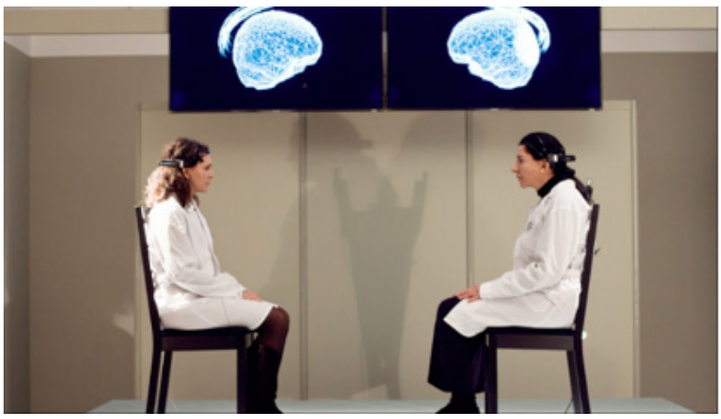
ABC Journal: We know that you've worked with the combination of neuroscience and art in the past, and are also working on some projects currently. What was your first encounter with the intersection of neuroscience and art? And what was your motivation to combine them?

Dikker: My first encounter was when I was working at the Sackler Institute for Developmental Psychobiology in New York. They were involved in organizing a summer workshop on consciousness which brought together artists, neuroscientists, therapists and general intellectuals. That took place at theatre maker Robert Wilson's house - Einstein on the Beach is probably his most known work. They brought Marina Abramovic there, who is a performance artist. She had just done the performance 'The artist is present' at the MoMA (Museum of Modern Art, New York) where she was sitting in front of the audience completely still, engaging in silent mutual gaze for anything between two minutes and eight hours. The neuroscientists who were there were very intrigued by the intense emotional reactions this performance stirred both in the audience and the performer. At the time, there was very little research on studying synchrony between two people. What we knew about social phenomena was mainly from showing people pictures and not the actual social interaction. So, we started brainstorming about restaging 'The artist is present' with Marina Abramovic as a neuroscience experiment in a museum and eventually implemented it. What we were interested in was studying the intense emotional reactions that were solely evoked by eye contact. More specifically, we asked what the relationship between eye contact and the feeling of being connected is, and to which extent brain waves become synchronised between the performer and an audience member or two audience members.

"Every work is an art piece, a science piece and more; because it's both at the same time."

Because it was in a museum, we wanted to create something around it that was going to be interesting for the museum audience as well. So, we developed a neurofeedback environment around the performance/experiment where people could watch along as their brain activity was displayed on two screens behind them. For that I worked with Lauren Silbert, who was at Princeton at the time. And that was my introduction to 'art and neuroscience'.

For me personally, I jumped at the occasion because I had done art in my own past. I've gone to the Gerrit Rietveld Academie, for example, and I've done conservatory for classical ballet. It's always been itching and that's probably one of the reasons why I, personally, jumped at it and none of my colleagues. So, that's how it began.



Measuring the magic of Mutual Gaze an Experiment and Art Performance

ABC Journal: The next question refers to a statement you made about art and neuroscience being mutually informative. Why would you say they are mutually informative rather than describing one as a tool for the other?

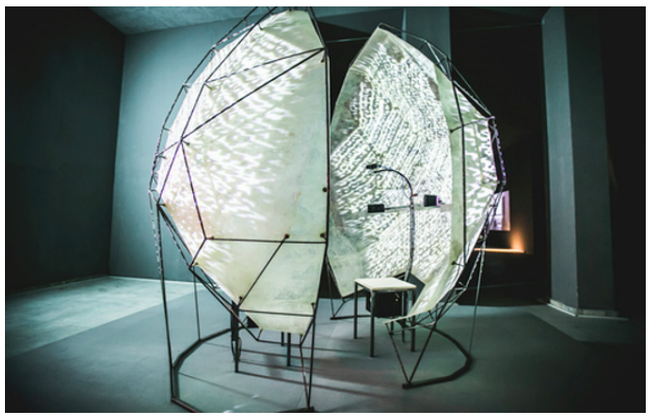
Dikker: That's just the way I want to engage in the intersection of art and neuroscience. I am not discarding work where people use art as a tool to teach neuroscience, for example, or make neuroscience tangible. Or the other way around, art about neuroscience. That's just not the kind of projects I personally want to realise. Personally, I keep on being rewarded by interdisciplinary conversation, where everybody has an equal seat at the conversation table, so to speak. You talk about what certain terms might mean in one field or another field and you're finding common ground. If you are, for instance, from neuroscience, you can go back to the laboratory and take these new forms of understanding with you in your own research. So, it's basically a tool to enrich yourself in all of the fields you're coming from. That's in terms of just the advancements and from a personal perspective. I find it very interesting and an exciting challenge to make works that don't just serve the other or vice versa, but we really try to balance it out so that every work is an art piece, a science piece and more; because it's both at the same time. Again, I want to emphasise that I don't think that's the way to do art and neuroscience, because I'm learning that almost everybody who is at the intersection has a different understanding of it.

"In the neuroscientist community there was a lot of skepticism in the beginning. But due to this, we really had to make sure that the analyses that we do and the data that we have are sound and solid, so that is a good thing."

ABC Journal: The next question ties into what you just explained, but maybe you can tell us more about the concrete advantages you see in that approach as opposed to more conventional research in the lab.

Dikker: Again, a politically important thing to say is that there is much value in doing neuroscience in the lab, I want to make that absolutely clear. But one way to use art installations is to bring neuroscience out of the laboratory. For example, we were able to collect brain data from thousands of people in the 'Mutual Wave Machine' because the experiment was disguised as an art installation. People knew it was an experiment of course, but they were very intrigued, as they were just museum visitors. That setup allowed us to reach a large audience and a socially more naturalistic situation. We were testing them in their habitat, so to speak.

It also allowed us to educate people in a very intuitive way about the neuroscientific process of conducting experiments, which turned out to be a bit of a 'by-product' of doing art and neuroscience. 'By-producture' is relevant and important because there is a lot of misconception about neuroscience among the general population. Especially when you see pictures of fMRI statistical maps, people might think that your brain has a spirituality hub and that this 'god spot' is blue or something like that. Deceptive is not the word, but the way neuroscience is portrayed and hyped up is confusing. So, it is very important to have the general audience engaging with the messiness of the process, so that they understand science as a process, too. A process that is about asking questions. It is also about finding answers, but most of what we do is about asking the questions in the end, right? So, that turned out to be a super valuable part as well.



On the left, the 'Mutual Wave Machine' installation.
Above, two participants interacting in the installation.

"The Mutual Wave Machine is an intimate audiovisual capsule that responds to shared brain activity of its audience. Two visitors at a time experience their brainwave synchronisation as they try to approach or distance themselves internally."

— **Matthias Oostrik**

ABC Journal: There is a spectrum of art and neuroscience with a lot of people and a lot of opinions into it; do you ever get personally criticised by artists or neuroscientists?

Dikker: In the neuroscientist community - not so much anymore, but definitely in the beginning. There was a lot of skepticism. People's initial instinct is that what you're doing is dabbling at the fringes, but you're not really doing science. That is actually a good thing, because it means that we were challenged to really make sure that we got the signal processing right. I work with hardcore engineers and scientists who make sure that the analyses that we do and the data that we have are sound and solid. I mean, I think the field is shifting toward taking it more seriously, but we're suffering a lot from - well, suffering is a very big word -, but there are many artists and general people who are now doing neuroscience research with the same equipment that we're using. There's a lot of bad science out there, so it's very stressful to stick a toe into that field. You realize you need to be careful not to be associated with pseudoscience. No criticism from the artistic community, actually. But it's funny, because the science community will call you an artist, but the art community will call you a scientist.

ABC Journal: Moving to our last question, what are your words of motivation to us as students? Obviously, we see your research and it's very inspiring, but most of us are not going to start an art installation anytime soon.

Dikker: Why?

ABC Journal: Because most of us probably don't have the courage to do this or are not sure if they can participate in these projects...

So, maybe YOLO[1] is the advice? I think in that sense I was very naive throughout most of the projects that I did, and I think that's what made it possible. For me, it was working with the challenges. That's a personal thing, but everyone should choose their own passion. Passion is important in our fields. If this is what you want to be doing, it's a very important thing to have. That and curiosity. The important thing is that those are in place if you want to be working in an interdisciplinary field. I don't know if it was courage, but for me, it was naiveté, more than anything - trying things out and knowing how to work with the limitations. For me personally, it is in the limitations where the enrichment happens. You try to move in a certain direction, and you hit the wall and then you try to figure out a way to make that wall work for you. If that makes sense?

"For me personally, it is in the limitations where the enrichment happens."

1 You only live once

Use of prosody to mark information structure in autistic female and male adults with high-level language ability.

Nina Parrella | University of Amsterdam

Prosody, a language domain involving stress, intonation and pitch, typically assists in conveying meaning and emotion. For individuals with autism, prosodic use has been described as striking and disorganised, seldom used to enhance communication (Green & Tobin, 2009; Nadig & Shaw, 2011). Recognition of variability of prosodic use within the autistic population is critical, however (DePape, Chen, Hall & Trainer, 2012). Primarily motivated by the presence of equivocal symptomatology in autistic females (Baron-Cohen & Wheelwright, 2004; Healthed, 2018), this investigation explicates part of prosody's heterogeneity through a sex comparison of autistic individuals with high-level language. To do so, suprasegmental features of speech (pitch and duration) were examined from recordings of semi-spontaneous conversations with female and male adults with and without autism. Explicitly, an analysis of new information marking in a sentence (focus) as opposed to already- established details in the conversational context (topic), in both sentence-initial and sentence-final positions was conducted. Results revealed that autistic females used greater noun duration than autistic males. Autistic females also used pitch-falls to mark information structure more meaningfully than female controls, autistic males and male controls, but did not use pitch-rises conventionally. Female controls were revealed to use comparatively larger pitch ranges in general, suggestive of melodious speech quality. This preliminary study suggests that, despite using smaller pitch ranges than female controls, autistic females may utilise certain valuable elements of prosody to enhance their communication more than autistic males.

Autism is a lifelong developmental disorder that presents variably and affects the way individuals perceive their environment and interact (National Autistic Society, 2015). Deficits in the pragmatic use of language in autism are well-documented (Young, Diehl, Morris, Hyman, & Bennetto, 2005; Wing & Gould, 1979) and indicate communication limitations and the presence of restricted interests (Baron-Cohen, 2002). Pragmatic ability in this population can be better understood through critical analysis of certain language constituents (Eigsti et al., 2011). According to Roach (2000), prosody (or intonation) serves essential communication functions at the pragmatic level. A principal component of an individual's pragmatic competency can therefore be grasped by measuring their prosodic ability, for instance, their usage of pitch and duration to mark information structure.

Vocally emphasising the focal information (i.e. focus word/s) in an utterance by using larger pitch range and longer duration than topic words can assist language comprehension for the listener while the antithesis could obscure communicative intent (Green & Tobin, 2009). Typical prosodic use marks focal information to a lesser extent in the sentence-final (object) position than in sentence- initial (subject) (DePape, Chen, Hall & Trainer, 2012). An inability to employ adequate pitch variation across an utterance is likely to result in a sense of general monotony (DePape, Chen, Hall & Trainer, 2012). Smaller prosodic contours and distinctly narrow, typical, or wide pitch ranges have been identified in autism (Green & Tobin, 2009). Other studies, namely Shriberg et al., (2001) and Peppé et al., (2011), have revealed that autistic individuals stress the initial parts of utterances regardless of their semantic value.

Shriberg et al. (2001) compared prosodic use in children (a combined sample of boys and girls) with autism to typically developing controls. They observed that the autistic group used less apposite prosodic phrasing, including misplaced lexical stress, slowed phrasing, and unusual resonance qualities (Wichmann, Dehé & Barth-Weingarten, 2009). More recently, DePape et al. (2012) conducted detailed analyses of prosodic pitch and duration usage in autistic male adults. While they found that both high-level language autistic and moderate-level language autistic groups used abnormal prosody, they highlighted that those with high-level language used generally exaggerated prosody but did not use pitch and duration to convey information structure communicatively, whereas those with moderate language function varied prosody less in general compared to controls, but did use pitch and duration communicatively to convey information structure (DePape, Chen, Hall & Trainer, 2012). Furthermore, in the only assessment of prosodic comprehension in autism, autistic male adolescents were compared to typically developing controls (Diehl, Bennetto, Watson, Gunlogson, & McDonough, 2008). This autistic group were poorer at using prosody to resolve syntactic ambiguities (Diehl, Bennetto, Watson, Gunlogson, & McDonough, 2008).

Due to the well-documented heterogeneity of prosodic use

in autism (Green & Tobin, 2009; DePape, Chen, Hall & Trainer, 2012), it would be unjustifiable to deem abnormalities in this language domain as diagnostically influential characteristics for autism. However, establishing more detailed evidence for the variable prosodic tendencies in autism has potential to valuably elucidate communication and language profiles of autistic subgroups. Overall, the cited research has favoured male participants, and in studies that included both sexes, no subgroup-analysis was conducted. Thus, a general lack of prosodic data from autistic females is apparent (Parish-Morris, 2017).

Prosodic differences related to emotion recognition have been identified between typically developing females and males, with females regarded more competent than males (Baron-Cohen & Wheelwright 2004). Relatedly, Doherty et al. (1995) investigated sex differences in emotional contagion, and found that typically developing females experienced the targets' emotional states more readily than males. No distinction was made between body language and prosody here however, and emotional contagion for the autism population was not studied. These limited and tenuously related outcomes cited tempt further questions. The current research hypothesises that females and males with and without autism use prosody differently.

Head et al. (2014) claimed that autistic females with IQ scores within the average range have demonstrated increased functional social behaviour compared to males with autism (Head, McGillivray, & Stokes, 2014). Moreover, it has been proposed that the preponderant prevalence of autism in males could be partially explained by sex differences in clinical symptoms (Baron-Cohen & Wheelwright, 2004). This suggests that while autistic males present with overt traits, female profiles are generally less visible clinically. As previously mentioned, autistic females show increased functional social behaviour compared to males (Head, McGillivray, & Stokes, 2014). Professor Tony Attwood (2018) describes autism with high language level as the invisible end of the spectrum for females. They are characterised as competent in avidly observing, analysing and imitating, resulting in successful masking of their social confusion in support of their pathological fear of making mistakes (Healthed, 2018). These intellectual, rather than intuitive, hiding techniques are also evident when reproducing sounds, whereby autistic females (with high-level language) have been reported to sing with perfect pitch and imitate accents well (Healthed, 2018). These findings allude to the notion that their prosodic use may also be more purposeful.

Needless to say, identification of autism in autistic females with high-level language is challenging when they present with stylised and contrived mannerisms that disguise traits (Healthed, 2018). If they are perceived by professionals as being more social, their presentation of symptoms may be misinterpreted and accurate diagnosis may be delayed (Halladay, et al, 2015). Furthermore, inadvertently anticipated male manifestations of autism in clinical settings can result in misdiagnoses, commonly experienced by autistic females (Baron-Cohen & Wheelwright, 2004). While autistic females with high-level language are considered 'expert mimics' (Healthed, 2018), it is yet to be determined whether these copying abilities translate to the language domain of prosodic use. Understanding if and how autistic females perform differently on specific prosodic production tasks could assist in deconstructing their social aptitudes and lead to alteration of expectations in clinical settings.

The research mentioned denotes relevance in pairing these two areas; heterogeneity of prosodic use in autism, and discrepancies in symptomology between males and females with autism. Secondarily, it may incidentally reveal variances between typically developing male and female controls. Extending on DePape et al.'s study on the use of prosody and information structure in adults with autism in relation to language ability, referential meaning is the principal constituent evaluated. More specifically, participant ability to emphasise new information in a sentence (focus) as opposed to the information already given in the conversational context (topic) is investigated through analysing pitch and duration (DePape, Chen, Hall & Trainer, 2012).

Both impaired general prosodic use and impaired marking of information structure would be expected to unhelpfully impact social communication and thereby lead to increased difficulty in personal domains, such as making and keeping friendships, and in professional domains, such as competing for employment opportunities. Understanding if and how autistic females and males perform differently on specific prosodic production tasks could assist in deconstructing their social aptitudes and lead to alteration of expectations in clinical settings. Striving to disentangle a small component of the broad ambiguity of sex-related variances in autism symptomatology, the current study has three fundamental areas of interest:

- use of absolute pitch and duration
- use of prosody to mark information structure, explicitly, the extent to which new information
- (focus nouns) were accentuated compared with information already provided (topic nouns)
- the relation between prosodic use and sex

Accordingly, the following hypotheses and corresponding predictions are posed:

1. Autistic males make less use of prosody than neurotypical individuals.
   - Prediction: The autistic male group will use smaller pitch ranges and shorter noun durations than both control groups.
2. Autistic females make less use of prosody than neurotypical individuals.
   - Prediction: The autistic female group will use smaller pitch ranges and shorter noun durations than both control groups.
3. Autistic females make more use of prosody than autistic males.
   - Prediction: The autistic female group will use larger pitch ranges and longer durations than the autistic male group.
4. Autistic males use less prosody to mark information structure than neurotypical individuals.
   - Prediction: The difference in pitch range and duration between focus and topic will be smaller in autistic males

than in both control groups.

5. Autistic females use less prosody to mark information structure than neurotypical individuals.
   - Prediction: The difference in pitch range and duration between focus and topic will be smaller in autistic males than in both control groups.
6. Autistic females make more use of prosody than autistic males to mark information structure.
   - Prediction: The difference in pitch range and duration between focus and topic will be larger in the autistic female group than in the autistic male group.

Materials and Procedure

Participants

Ten adult participants (M = 22.5 years; range = 16-34 years) with diagnoses of autism were assessed. Of these ten, five were female and five were male. Autistic participants reported being diagnosed through several standard assessment batteries. These were the Autism Diagnostic Observation Schedule, the Autism Diagnostic Interview - Revised (ADOS and ADI-R; Lord et al., 1989, 1994) or the Diagnostic Interview for Social and Communications Disorders (DISCO; Leekam et al. 2002). Participants carried formal psychiatric diagnoses of either 'Asperger syndrome' or 'autism spectrum disorder (ASD)'. Approximate age of diagnosis for female participants (M = 23 years) was later than for male participants (M = 14 years). Three potential participants (two female, one male) were excluded due to not having received formal diagnoses of autism.

Autistic participants were matched in age and language level in order to best isolate sex- related differences in prosodic abilities (Lai et al., 2011). All participants were verbally fluent, and achieved receptive vocabulary scores of 100%, as measured by the Receptive Language Assessment with Splingo (4-word level, e.g. object-preposition-adjective-location, person-action-preposition- location), used to indicate general language functioning (The Speech and Language Store, 2018). Ten subjects (five female, five male) showing neurotypical development (normal controls, NC groups) were also tested (M = 25.3 years; range = 20-30 years) to provide a standard for comparison purposes. Participants completed a questionnaire on languages spoken and family history of autism, whereby none of the participants in the NC groups had a family member diagnosed with autism. All participants were monolingual English-speakers and the groups were matched in age ($F<1$). The sample contained accent variation, including Australian, New Zealand and several British accents.

Procedure

The research was approved by the University of Amsterdam Ethics Committee of the Faculty of Humanities and conformed to the principles set out in the European General Data Protection Regulation (GDPR). All participants provided informed consent. Testing lasted approximately 45 minutes and took place in settings including educational institutes, participant homes, as well as via Skype phone calls. Participants were debriefed immediately after completing the study.

Participants were asked questions about pictures presented in an adaptation of Chen's (2011) "Under the Shape" game, a paradigm designed to be structured yet interactive. Like in Chen's (2011) "Under the Shape" game, a *Familiarization Phase* was administered to ensure that participants recognised and used a consistent label for each picture (DePape, Chen, Hall & Trainer, 2012). They were asked to name a series of pictures of people, animals, or objects, then instructed to use them to the same pictures in the *Experimental Phase*. The *Experimental Phase* involved the administration of the "Under the Shape" game. Each exercise contained a pictured scenario, whereby two familiar referents (from the familiarisation phase), were simultaneously presented on the screen. One was be covered by an opaque shape (DePape, Chen, Hall & Trainer, 2012). A *who* or a *what* question was then asked (using consistent prosody, with prominence placed on the question word), before the rectangle was removed to reveal the information required for the participant to generate their verbal response (Figure 1). Each scenario necessitated either a *who* or *what* question from experimenter and corresponding responses from participant.

Target responses to *who* and *what* question types differed in relation to whether the nouns carrying new information (focus) occurred in the sentence-initial position (subject) and the given information (topic) in the sentence-final (object) position or vice versa (DePape, Chen, Hall & Trainer, 2012). Placement of subject and object remained in the same sentence locations, subject at beginning, object at end. Consequently, the focus and topic of the sentence should shift without syntactic reorganisation. For example, when "*Who* is having a bath?" is asked, the new information (focus) occurs in the initial position, "The *cat* is having a bath" (Figure 1). Contrastingly, when "*What* is the cat wearing?" is asked, the new information (focus) occurs in the final position, "The cat is wearing the *shirt*" (Figure 2). Participants were instructed to respond in full, meaningful sentences. This allowed for a subject in the sentence-initial position and an object in the sentence- final position to be examined for each scenario.

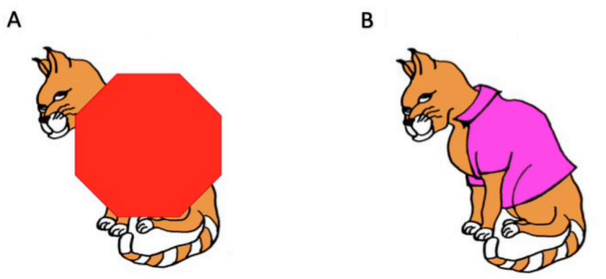


FIGURE 1 | Example trial of initial topic and final focus. (A) Experimenter: "*What* is the cat wearing?" (shape disappears to reveal a picture of a shirt) (B). Participant: "The cat is wearing a *shirt*."

Participants responded to 22 trials in the experimental phase, with equal numbers of who and what questions (DePape, Chen, Hall & Trainer, 2012). This design allowed for acoustic analyses to

compare the same nouns across different contexts, as all nouns served both topic and focus functions. Obtaining three measurements for each noun (range-rise, range-fall and noun duration), the variation of acoustic features across topic and focus nouns were examined. Each combination of subject and object nouns took place once during the experiment. Acoustic analysis could then be performed to examine verbal responses, measuring how they vary prosody according to two variables, *information structure* (topic/focus), and *sentence position* (initial/final).

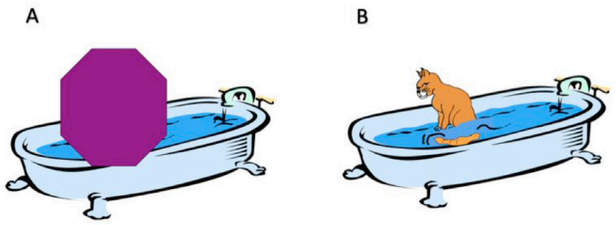


FIGURE 2 | Example trial of initial focus and final topic. (A) Experimenter: "*Who* is having a bath?" (shape disappears to reveal a picture of a cat) (B). Participant: "The *cat* is having a bath."

Acoustic Annotation

To prepare data for acoustic analysis, the shape of the pitch contour for subject and object nouns was annotated. Regardless of noun function (topic/focus) within each sentence, sentence-initial nouns were referred to as 'subject' while sentence-final nouns as 'object'. While most nouns contained rise-fall contours, they varied in the extent to which the pitch rose and fell. The difference between the peak and the preceding lowest pitch value is referred to as 'range-rise' and difference between the peak and the proceeding lowest pitch value range-fall as 'range-fall' (DePape, Chen, Hall & Trainer, 2012). Noun waveforms and duration were acoustically annotated using the wide-band spectrum and pitch track in Praat 5.1.0.7 (Boersma and Weenink, 2009). Each noun was labelled with three fundamental frequency (F0) and two segmental markers (Figure 3):

- Initial F0 minimum: the initial lowest pitch insubject noun (L1) and object noun (L4).
- F0 maximum: the highest pitch in the subject noun (H1) and in the object noun (H2) before the beginning of the pitch fall.
- Final F0 minimum: the lowest pitch reached following the F0 maximum in the subject noun (L2) and in the object noun (L5).
- The beginning of the noun: b1 and b2 marking the start of the noun-initial phoneme in the subject noun and in the object noun, respetively.
- The end of the noun: e1 and e2 marking the end of noun-final phoneme in the subject noun and in the object noun, respectively.

When labelling the F0-related landmarks, precautions were taken to avoid the limitations of automated pitch measurements (octave errors). During the annotation process, it became apparent that supraglottal/voiceless sounds, without true glottal/voiced periods (considered the harmonic components of the signal/oscillation of the vocal folds), became pitch candidates (Elie & Chardon, 2018). Fricatives, affricates and bursts in stop consonants were discarded as residual noise (Elie & Chardon, 2018). These spurious micro-prosodic pitches were evaded by setting the pitch ceilings to 400Hz, and manually searching for the F0 of the accented vowel. Three measurements were obtained for each noun:

- Range-rise: H1-L1 for subject nouns and H2-L4 for object nouns.
- Range-fall: H1-L2 for subject nouns and H2-L5 for object nouns.
- Noun duration: Timee1 -Timeb1 for subject nouns and Timee2 - Timeb2 for object nouns.

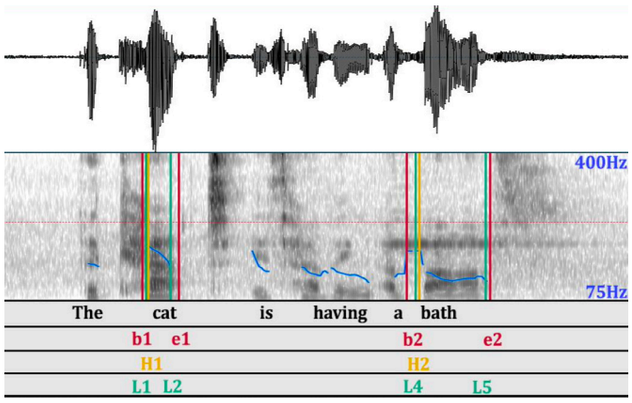


FIGURE 3 | Acoustic analysis. The sentence "The *cat* is having a bath" was produced as an answer to the question "*Who* is having a bath?" by an autistic female speaker. The landmarks in the subject noun "cat" and the object noun "bath" are the following: F0 minimum in the rising portion (L1/L4), F0 maximum (H1/H2), F0 minimum in the falling portion (L2/L5), beginning of the word (b1/b2), and end of the word (e1/e2).

Statistical Analysis and Results

Initially, an analysis of variance (ANOVA) was administered for absolute pitch to establish whether groups used comparable pitch levels across sentence position. The lowest values preceding the pitch peak in each noun (L1 for subject noun and L4 for object noun) represented absolute pitch. L1 of each subject noun and L4 of each object noun served as the dependent variable, sentence position (subject, object) as a within-subjects variable, and group (female controls, male controls, autistic females, autistic males) as a between-subjects variable (DePape, Chen, Hall & Trainer, 2012).

An ANOVA was also used for absolute duration to establish whether groups used comparable noun durations across sentence position. Duration of subject nouns (e1-b1) and object nouns (e2-b2) served as the dependent variable, group (female controls, male controls, autistic females, autistic males) as a between-subjects variable, and sentence position (subject, object) as a within-subjects variable (DePape, Chen, Hall & Trainer, 2012).

To analyse information structure, ANOVAs were conducted with each of the following discrete dependent measures: subject

noun range-rise, subject noun range-fall, subject noun duration, object noun range-rise, object noun range-fall, and object noun duration (DePape, Chen, Hall & Trainer, 2012). Each ANOVA was conducted with noun (20 pairs) and information structure (topic, focus) as within-subject variables and group (female controls, male controls, autistic females, autistic males) as a between-subjects variable (DePape, Chen, Hall & Trainer, 2012).

Two types of planned pair-wise comparisons were then administered to the data. Topic and focus nouns were considered separately using Mann-Whitney U tests, which determined whether groups contrasted in range-rise, range-fall, and duration. To establish whether each group used prosody to differentiate between topic and focus nouns, planned Wilcoxon signed-rank tests were used for each dependent measure. To ascertain how acoustic features varied across topic and focus, the same nouns were compared directly, ensuring direct comparison of the same intrinsic vowel pitches.

Pitch and Duration

The two-way ANOVA conducted on absolute pitch revealed a main effect of group, $F(1, 3) = 32.86$, $p = <.0001$ ($\eta^2 = 0.230$), with the female control group using the highest pitch values overall. No significant effect of sentence position was established however, $F(1, 3) = 2.57$, $p < 0.11$ ($\eta^2 = 0.006$), despite pitch falling from sentence-initial (M = 174.71 Hz) to sentence-final nouns (M = 168.209 Hz). A significant interaction effect between group and sentence position was obtained, $F(1,3) = 53.4$, $p = <.0001$ ($\eta^2 = 0.373$).

The two-way ANOVA conducted on absolute duration revealed a significant effect of sentence position, $F(1, 3) = 70.93$, $p = <.0001$, ($\eta^2 = 0.235$), with shorter durations for the subject (M = 0.45s), than for the object nouns (M = 0.58s). A significant effect was also established of group, $F(1, 3) = 20.22$, $p = <.0001$, ($\eta^2 = 0.201$). No significant interaction between group and sentence position ($F < 1$) was established.

Post hoc tests using Tukey's (honestly significant difference) HSD showed that there was no statistically significant absolute difference between subject and object noun durations used by male controls and female controls. A significant absolute difference ($p < .05$) between subject and object noun durations used by the female control group and the autistic female group was revealed, with female controls using the longest noun durations. Statistically greater differences ($p < .01$) were found between subject and object noun durations used by female controls and autistic males, as well as between male controls and autistic females, male controls and autistic males, and between autistic females and autistic males.

Sentence Initial (Subject)

Initial range-rise

For initial (subject) position, the ANOVA on range-rise revealed main effects of group, $F(1, 3) = 9.71$, $p = <0.0001$, $\eta^2 = 0.23$ **(Figure 4A)**.

For focus nouns, Planned Mann-Whitney tests revealed that the female control group used significantly larger range-rises than both the autistic female group ($U = 17$, $p = .01$, $r = 0.54$) and autistic male group ($U = 17$, $p = .01$, $r = 0.54$). For topic nouns, the female control group used significantly larger range-rises than the male control group, ($U = 9$, $p = .002$, $r = 0.68$) and the autistic male group, ($U = 14$, $p = .007$, $r = 0.59$). The female autistic group also used significantly larger range-rises than the male control group, ($U = 14$, $p = .007$, $r = 0.59$).

Planned Wilcoxon signed-rank tests revealed significantly larger range-rises for topic than focus in the autistic female group ($Z = -2.8$, $p = .005$).

In sum, compared to the other groups, the female control group used larger range-rises for both focus and topic nouns. Both female groups exhibited larger range-rises for topic nouns, while male groups used larger range-rises for focus nouns.

Initial range-fall

For initial (subject) position, the ANOVA on range-fall revealed main effects of group, $F(1, 3) =$

8.41, $p = <0.0001$, $\eta^2 = 0.22$ **(Figure 4B)**.

For focus nouns, Planned Mann-Whitney tests found no significant differences in range-fall for any group. For topic nouns, however, the female control group used significantly larger range- falls than the male control group, ($U = 7$, $p = .001$, $r = 0.71$), the autistic male group, ($U = 6$, $p = .001$, $r = 0.71$) and (to a lesser degree) the autistic female group, ($U = 19$, $p = .02$, $r = 0.51$).

Planned Wilcoxon signed-rank tests revealed significantly larger range-falls for focus than topic in the autistic female group ($Z = -2.2$, $p = .02$) and the male control group ($Z = -2.2$, $p = .02$).

In sum, the female control group had the largest range-falls, with slightly larger range-rises for their topic nouns. All three other groups similarly used larger range-falls for focus nouns compared to topic nouns in initial position.

Initial duration

For duration of the subject noun, the ANOVA revealed a significant main effect of group, $F(1, 3) = 12.24$, $p = <0.0001$, $\eta^2 = 0.32$ **(Figure 4C)**. No main effect of information structure was found.

For focus nouns, Planned Mann-Whitney tests found that the autistic male group used significantly shorter noun duration than the male control group ($U = 18$, $p = .019$, $r = 0.51$), and the autistic female group ($U = 10.5$, $p = .003$, $r = 0.64$). For topic nouns, the autistic male group used shorter noun duration than the female control group ($U = 22$, $p = .03$, $r = 0.46$), the autistic female control group ($U = 9.5$, $p = .002$, $r = 0.67$) and the male control group ($U = 17$, $p = .01$, $r = 0.53$). Planned Wilcoxon signed-rank tests did not reveal statistically significant differences between initial topic and focus durations used by any group

In sum, the autistic male group used the shortest initial noun durations for both focus and topic nouns, while the autistic female group had the largest durations. Control groups used observably similar initial noun durations. All four groups used observably longer noun durations for focus nouns compared to topic nouns.

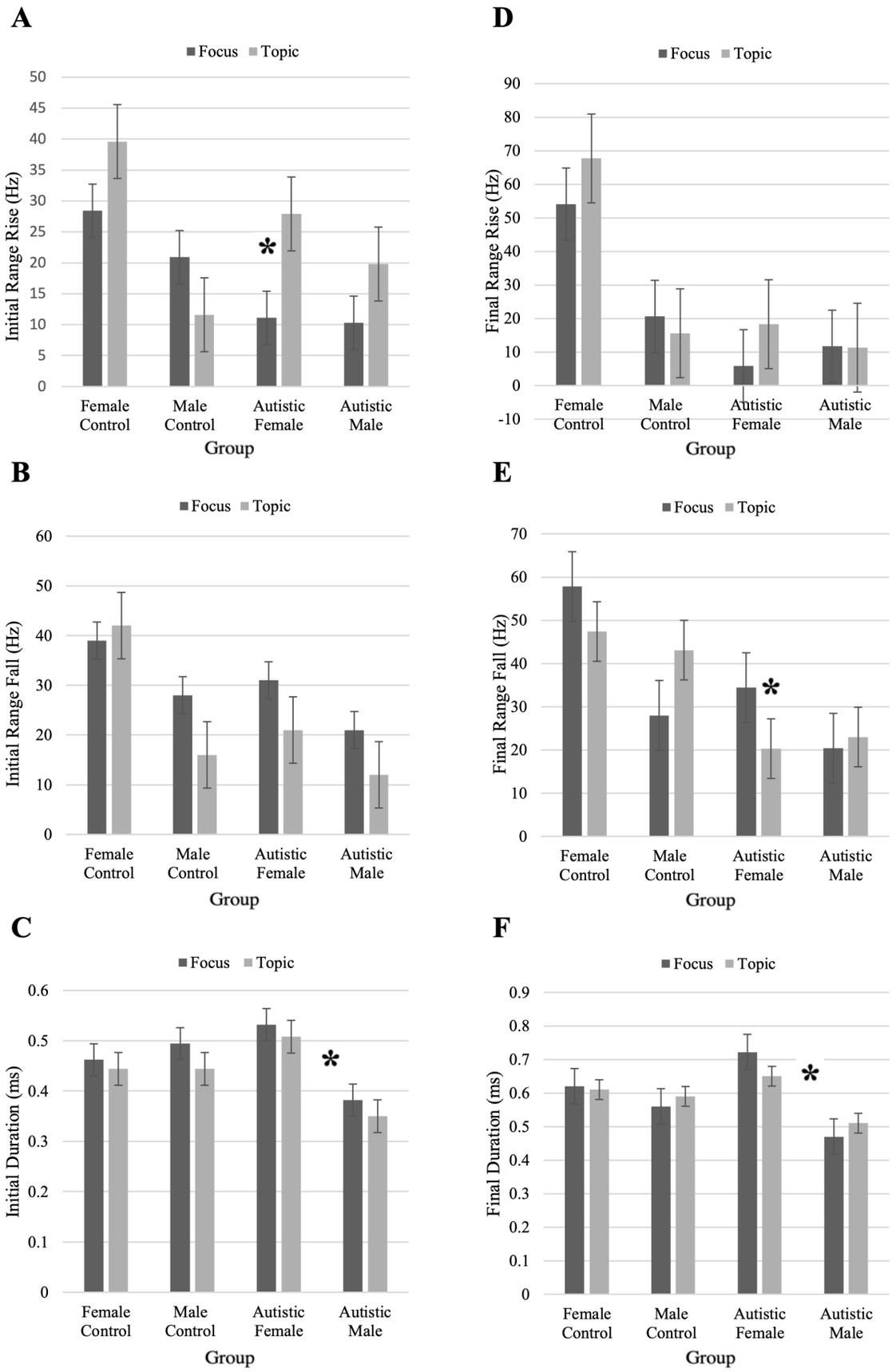


Figure 4 | Sentence-initial and sentence-final results. (A) Mean sentence-initial range-rise and SE by group. (B) Mean sentence-initial range-fall and SE by group. (C) Mean sentence-initial duration and SE by group. (D) Mean sentence-final range-rise and SE by group. (E) Mean sentence-final range-fall and SE by group. (F) Mean sentence-final duration and SE by group.

Sentence Final (Object)

Final range-rise

In the final (object) position, the ANOVA on range-rise revealed a significant effect of group, F (1, 3) = 12.51, p = <0.0001, η^2 = 0.34 (Figure 4D). No main effect of information structure was found.

For focus nouns, Planned Mann-Whitney tests revealed that the female control group used significantly larger range-rises than the autistic female group, (U = 18, p = .019, r = 0.51). For topic nouns, however, the female control group used larger range-rises than the male control group, (U = 21, p = .03, r = 0.46) and the autistic male group, (U = 17, p = .01, r = 0.53). Planned Wilcoxon signed-rank tests did not reveal statistically significant differences between topic and focus for range-rise used by any group.

In sum, the female control group used significantly larger range-rises than all other groups. Despite a great difference in rise, both female groups used observably larger rises for their topic nouns compared with their focus nouns.

Final range-fall

In the final (object) position, the ANOVA on range-fall revealed a significant effect of group, F (1, 3) = 6.33, p = <0.0009, η^2 = 0.19 (Figure 4E). No main effect of information structure was found.

For focus nouns, Planned Mann-Whitney tests revealed the female control group used significantly larger range-falls than the male control group, (U = 15, p = .009, r = 0.58), the autistic female group, (U = 23, p = .04, r = 0.44) and (to the greatest extent) the autistic male group, (U = 4, p = .0005, r = 0.7). Similarly, for topic nouns, the female control group used significantly larger range-falls than the autistic female group, (U = 17, p = .01, r = 0.53) and (to the greatest extent) the autistic male group, (U = 19, p = .02, r = 0.51). Planned Wilcoxon signed-rank tests revealed statistically significant differences between topic and focus for range-fall used by the autistic female group (Z = -2.8, p = .005).

In sum, the female control group used the largest range-falls for sentence-final nouns. Like the autistic female group, their focus nouns had larger range-falls than topic nouns, while both male groups had larger range-falls for their topic nouns compared with their focus nouns. The range-falls for focus words used by the autistic female group were notably larger than their topic words.

Final duration

For duration of the object noun, the ANOVA revealed a significant main effect of group, F (1, 3) = 8.86, p = <0.0001, η^2 = 0.26 (Figure 4F). No main effect of information structure was found.

For focus nouns, Planned Mann-Whitney tests found that the female control group used significantly longer final noun durations than the autistic male group, (U = 17, p = .01, r = 0.53). The autistic male group also used significantly shorter durations than the male control group, (U = 22, p = .037, r = 0.44) and the autistic female group, (U = 8, p = .001, r = 0.69). The autistic female group used significantly longer noun durations than the male control group, (U = 21, p = .03, r = 0.46). For topic nouns, a significant difference was detected between the autistic female group and the autistic male group, (U = 16.5, p = .01, r = 0.53), with the females using longer final noun durations than males. Planned Wilcoxon signed-rank tests did not reveal statistically significant differences between final topic and focus noun durations used by any group.

In sum, for sentence-final nouns, the autistic male group used the shortest durations, while the autistic female group used the longest (Figure 4F). The topic nouns used by both male groups were longer than their focus nouns, while the autistic female group used observably longer durations for their focus nouns compared with their topic nouns. The female control group used longer durations than the male groups, with very similar durations used for topic and focus nouns.

Discussion

Communication exchanges can be enhanced when individuals mark new informative details differently to the information previously established. As explained earlier, inspecting if and how this is executed by subgroups with and without autism is central to this research, with principal uncertainty surrounding whether autistic individuals use prosody to mark information structure precisely. Precise marking of information structure involves larger pitch-falls for focus than topic nouns in both sentence-initial (subject) and sentence-final (object) positions, and larger pitch-rises for focus than topic nouns in sentence-final positions (DePape, Chen, Hall & Trainer, 2012).

Despite each group consisting of only five participants, detailed acoustic analysis identified several robust and discernible performance disparities between groups. Firstly, the groups differed in their initial starting pitch (absolute) with female groups using higher pitch than male groups. Absolute duration results revealed that female groups also used larger noun durations for both topic and focus nouns than male groups. Overall, the smallest pitch ranges were used by the autistic male group, a prosodic style that can be deemed consistent with a monotonous speech quality (DePape, Chen, Hall & Trainer, 2012). Contrastingly, the significantly larger pitch ranges revealed in the female control group are suggestive of a melodious and varied speech quality (DePape, Chen, Hall & Trainer, 2012). The autistic female group and male control group also used smaller pitch ranges than the female control group, implying that their voices were unlikely to sound musical. These findings support the first hypothesis; that autistic males use smaller pitch ranges and shorter noun durations than controls, and one component of the second hypothesis; that autistic females use smaller overall pitch ranges than female controls but not male controls. Furthermore, an aspect of the third hypothesis was also addressed; that autistic males use shorter noun durations than autistic females. However, autistic males were not found to use significantly smaller pitch ranges than autistic females.

Notable global pitch performance differences between con-

trol groups are also visible, with the female control group using significantly larger range-rises and range-falls than the male control group, irrespective of information structure. The female control group's use of larger pitch range could support the notion that their pragmatic language abilities may be greater than those of males (Halladay, et al, 2015). Like the male groups, the autistic female group varied their pitch to a lesser extent than female controls; an attribute that could communicate a lack of engagement during interaction and partly supports the second hypothesis; that autistic females use smaller pitch ranges than female controls. Despite use of larger pitch ranges overall, the female control group did not use pitch to mark information structure in most sentence positions (with the apparent exception of final range-falls, that did not reach significance **Figure 4E)**. This finding negates the fifth hypothesis; that female controls use prosody to mark information structure more effectively than autistic females. It is undetermined whether unvaried speech might surpass appropriate marking of information structure for listeners.

Using pitch-falls to emphasise focal information is considered a principal marker of information structure in West Germanic languages (Chen, 2009). The autistic female group used pitch to mark information structure in both sentence-initial and sentence-final position by using larger pitch-falls for focus than topic nouns. Thus, in regard to this particular marking method, the autistic female group used the most precise prosody to communicate in this controlled yet interactive paradigm. Consequently, this finding does not support the fifth hypothesis; that autistic females use less prosody to mark information structure than neurotypical individuals. It is partly in favour of the sixth, however, as autistic females made more use of pitch-falls than autistic males to mark information structure. In sentence-initial position, however, the autistic female group used larger pitch-rises for topic than focus nouns, suggesting that their correct marking of information structure did not generalise to pitch-rises. Stressing the initial parts of utterances regardless of their semantic value, a tendency previously observed in autistic individuals (Shriberg et al., 2001; Peppé et al., 2011), was apparent for both autistic female and autistic male groups, who used larger pitch-rises and longer noun duration for subject nouns than object nouns.

An outcome inconsistent with DePape et al. (2012), concerned noun duration. Here, the autistic female group used longer noun duration in both initial and final positions compared with other groups. Despite not reaching statistical significance, it is conceivable that the autistic female group used duration to mark information structure in both sentence positions, which would support the fifth hypothesis; that autistic females make more use of prosody to mark information structure than autistic males but not the second; that autistic females make less use of prosody than neurotypical individuals. Needless to say, noun duration used by autistic females and males warrants further investigation.

While entire utterance length was not specifically measured for comparison, shorter noun duration, as detected in the autistic male group, could be indicative of faster overall speech rate. It is uncertain whether this acoustic feature can be viewed as a characteristic in autism, however, evidence for deficit in conversational entrainment (a developmentally acquired skill), whereby individuals match their speech rate to their communication partners, has been identified in autistic adults (Wynn et al., 2018). Wynn et al. (2018) propose that such conversational weakness could contribute to the social struggles endured by this population.

An inability to use pitch to mark information structure has been hypothesised to reflect working memory limitations and trouble combining acoustic and linguistic structure over the course of an utterance (DePape, Chen, Hall & Trainer, 2012). It could also be argued, however, that when focal information is not emphasised in the conventional manner, nuanced techniques that may subtly highlight certain words can be used instead. It is suggested that such idiosyncrasies in marking information structure may not indicate poor communication skills overall, and that correct marking of information structure could also be considered unnaturally 'over-precise'. Previous deliberations surrounding similar outcomes have suggested that high-level language ability (as autistic participants in this study presented with) could also indicate more categorical understanding of language that could alter typical prosodic use. For instance, during assessment, it was noted that two male autistic participants expressed confusion surrounding the incongruousness of certain paired images in trials by responding to multiple questions with 'question-like' inflection, using range-rises for object nouns.

It would be astute to question whether autistic females are typically exposed to more experiences of variation in acoustic cues than autistic males, allowing them to develop their comprehension as listeners. If autistic females spend more time with females (who ostensibly use larger pitch ranges), it could be conjectured that they model their speech behaviours on prosody with amplified melodic characteristics. It could be argued that the way that the female control group varied pitch with respect to information structure was not useful to listeners, however. This arbitrary and impractical use of large pitch exertions that fails to direct attention to focal information could confuse listeners whose comprehension could be enhanced by classical use of pitch rises and falls.

Several anecdotes recorded from informal conversation with participants usefully contribute relevant details to this theme. An autistic female participant shared that while she has a conscious proclivity to imitate voices, she does not recognise or appreciate the value in altering pitch levels during interactions. This admission sparks questions surrounding prosodic comprehension abilities in autistic females, suggesting that their expressive prosodic abilities could surpass their receptive skills. Three autistic male participants reported knowledge of early language delay whereas none of those in the autistic female group did so. The later diagnoses in general in the autistic female group does suggest that language abnormalities early on were less detectable. Three autistic female participants divulged that prior to formally realising they were autistic, they wrongly acquired other diagnoses, which included borderline personality disorder, schizophrenia and major depressive disorder.

Certain aspects of this study could be improved in future research. Despite the identification of multiple differences across groups, the sample size was not large enough to allow for outlier analysis. Also, while the experimental paradigm was intended for controlled yet interactive communication, it is possible that the participants did not use prosody consistent with their usual conversing style due to the pressures of investigational settings and expectations. Analysis of spontaneous samples may have provided clearer insights into natural prosodic use. Another major obstacle when examining autistic subgroup symptomatology is that diagnostic definitions vary. When concerned with autism with Asperger's profile (higher-level language), individuals may have received varying diagnostic titles, including high-functioning autism, Asperger syndrome and autism spectrum disorder (ASD) (Diehl et al., 2009). Moreover, navigating variations in reported indicators (for instance, presence of an early language delay) when grouping participants can be disorderly. Thus, grouping based on specific cognitive abilities was considered the most reliable method. However, using merely a receptive language screening tool could be deemed insufficient for grouping of global language level. A more thorough evaluation of speech and language functioning (encompassing articulation, phonological processing, syntactic and semantic skills) would be highly valuable.

This study recognises current limitations in understanding the superficially superior socio- communication abilities in females with autism (Lai et al., 2011) through an attempt to ascertain empirical evidence for distinctions between the sexes in prosodic use, a constituent of pragmatic language that is widely identified as compromised in autism (Peppé, 2006). Regardless of whether listeners knowingly detect atypical prosodic cues for information structure, unpredictable communication styles may be more susceptible to scrutiny. Such judgements could result in unfavourable social implications for speakers.

In conclusion, systematic analyses of prosodic pitch and duration usage in adults with and without autism found that compared to both control groups and autistic males, the autistic female group used range-falls and duration communicatively to convey information structure in both sentence positions. Affirming specified components of the first, third, fifth and sixth hypotheses, the autistic male group varied prosody less in general compared to the female groups, used shorter overall noun durations, and did not use range-falls or duration to convey information structure, unlike autistic females. These outcomes suggest that at least some of the heterogeneity of prosodic use among adults with autism could be related to sex, where females make more use of certain prosodic features and functions than males do.

While it remains unclear as to whether the prosodic differences identified stem from varied genetic aetiologies, diverse social expectations, or experiences with therapeutic language interventions, this research serves as a valuable starting point for appreciating how prosodic profiles might surface differently for autistic males and females. Preliminary findings that autistic females use smaller pitch ranges than typically developing females, yet more precise marking of information structure through the use of larger pitch-falls could be clinically valuable information if reaffirmed through further investigations. Unveiling specific behavioural phenotypes that vary between females and males with and without autism could lead to developing sex-specific cognitive criteria for defining and supporting autism (Attwood, 2007). This would be of particular value to autistic females, a neglected yet essential population (Healthed, 2018).

References

Neuroaesthetics:
Grounded in Science or Merely Aesthetically Pleasing?

Marta Stojanovic

Beauty in the Eye of the Beholder

Imagine you are strolling through an art gallery. Perhaps you wonder how your brain lights up in response to the works on display, including which regions harbour the most admiration for an oil-on-canvas by Lucian Freud or gain most enjoyment from a soft impressionist landscape by Monet? Alternatively, imagine you are listening to a classical music piece. Perhaps you wonder which neurons act as music aficionados, or which synapses double as Mozart enthusiasts?

If you have ever had such musings while passively appreciating various arts, you are not alone. Semir Zeki is a prominent researcher at University College London (UCL) who explores the neurobiology of beauty. Zeki's main interest lies in the neural basis of art appreciation, and his research has focused on the subjective appreciation of visual, auditory to mathematical beauty (Kawabata & Zeki, 2004; Zeki, Romaya, Benincasa and Atiyah, 2014).

Zeki's investigations follow a century-long debate among philosophers on whether beauty can be quantified. As there is no single or universal standard for beauty, the focus turns to how it is experienced by each individual subject as the subjective experience (Zeki, 2012). Even the greatest artworks are sometimes cast sub-standard or opaque depending on the observer, and it seems that beauty may truly be in the eyes of the beholder, even within the scope of science.

Beauty in the Scanner

Zeki utilizes neuroimaging techniques such as fMRI to help elucidate which brain regions are active during the subjective experience of beauty. In Kawabata and Zeki's (2004) well-cited study, subjects rated a vast number of paintings across different picture categories such as abstract or still-life as beautiful, neutral or ugly, first before scanning. In the scanner, subjects sorted the same stimuli with button presses into one of the three aforementioned categories. Judgment-related activity in brain regions was compared between 'beautiful', 'ugly' and 'neutral' ratings.

Most pertinent to Zeki's claim regarding the brain basis of art appreciation, activity in an area of the medial orbitofrontal cortex (mOFC), mainly field A1 (A1mOFC), seemed to correlate with beauty ratings given by participants. The finding has since been replicated for different forms of visual or auditory art, the perception of attractiveness, and beauty comparison between stimuli (Gallace & Spence, 2011; Jacobs, Renken & Cornelissen, 2012; Kedia, Mussweiler, Mullins & Linden, 2013).

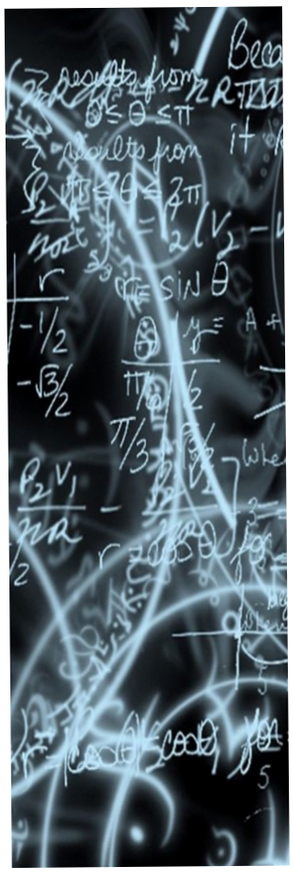
On the opposite end of the continuum, Kawabata and Zeki (2004) also found a correlation between brain activity and ugliness, with decreased activity in the mOFC paired with an increase

The Artist's Garden at Giverny, 1900 by Monet.

in motor cortex activity. The activation seemed to extend to the amygdala and other areas of the motor system, which Zeki jokingly, but not entirely unfoundedly, claimed may be in an effort to run and protect yourself from the perceived ugliness (Dougherty et al., 1999; Armony & Dolan, 2002). Overall, the higher the subjective rating of beauty, the greater the observed change in mOFC activity, and the other way around for unpleasant stimuli or perceived ugliness.

Math is Beautiful!

The study of neuroesthetics has been expanded to the more nuanced domain of mathematical beauty, as one of Zeki's newer pursuits. Zeki et al. (2014) scanned the brains of fifteen mathematicians while they viewed mathematical formulae they previously rated as beautiful, neutral or ugly. The experience of mathematical beauty, inferred from the subjective ratings, also correlated parametrically with activity in the mOFC, where an increase in activity correlated with greater reported beauty. The mathematicians in the study were hypothesized to have perceived the equations as beautiful because their experience trained them to see their intrinsic beauty. Zeki, Chen and Romaya (2018) distinguished between biological and artefactual beauty, where biological beauty is predetermined by innate brain concepts that are



Bitar (2019)

$$e^{i\pi}+1=0$$

Euler's Identity
(Zeki et al., 2014)

$$\frac{1}{\pi}=\frac{2\sqrt{2}}{9801}\sum_{k=0}^{\infty}\frac{(4k)!(1103+26390k)}{(k!)^4 396^{4k}}$$

Ramanujan's infinite series for 1/ϖ
(Zeki et al., 2014)

resistant to change, while artefactual beauty develops after birth and is modifiable through experience (Zeki et al., 2018; Zeki & Chen, 2020). Artefactual beauty therefore has greater inter-individual variability and is, apparently, far more malleable. Zeki et al.'s (2014) findings suggest that mathematicians do not merely use formulae blindly or in a goal-oriented way, but instead may harbour the same kind of profound reaction to them as a sommelier to an old bottle of full-bodied red or an avid comic strip collector to a classic Marvel issue.

Is Math Really Beatiful?

The assertion that mathematics is beautiful may be hotly disputed by many for a number of reasons, and, scientifically, Zeki's claims have been extensively questioned. Apart from the regular suspect of small sample size in Zeki et al.'s (2014) study with mathematicians, there were few 'ugly' ratings. In one session, only two of the formulae out of sixty were rated as 'ugly', which does not seem to provide a solid basis for comparison. The study furthermore did not test whether and to what extent the mathematicians perceived beauty in objects, faces or other stimuli they were not experts in. Moreover, the A1mOFC activity observed was relative activation, where the mOFC was in fact an area of deactivation, in which greater relative activity was found for 'beautiful' compared to 'ugly' or 'neutral' stimuli. Understanding that Zeki's claims about the role of the mOFC are based on relative activation makes them slightly less appealing or convincing.

As is often the case, the important distinction between causation and correlation comes into play, too. For instance, studies have previously found a link between mOFC activity and reward processing. The mathematicians' beauty ratings correlated with the level of understanding of the equation, so reward processing could serve as an alternative explanation. For example, the most consistently highly-rated formula was Leonhard Euler's identity, while a formula consistently rated as ugly was Srinivasa Ramanujan's infinite series for 1/ϖ, with a possibly more elaborate look.

Was relative activity in the mOFC lower for worse-understood formulae because there was greater concordant activity in visual areas while the mathematicians processed the formulae? Was the activity to do with reward processing upon correctly identifying and processing the formulae or was it due to potential perceived elegance in simplicity? These questions make it difficult to reliably attribute mOFC activation solely to beauty perception.

Similar doubts or considerations can be applied to Zeki's earlier studies. Kawabata and Zeki (2004)'s popular paper includes two main procedural concerns (Capo, Cela-Conde, Munar, Rossello and Nadal, 2008). First, the study involved a stimuli pre-selection procedure where participants first rated the pictures outside the scanner. This may have inadvertently activated recognition processes when subjects repeated the task while brain activity was recorded, as previous studies have found an association between mnemonic processes and aesthetic preference (Cela-Conde et al., 2002; Nadal et al., 2006). A second concern is to do with the preparation of stimuli. A number of variables have been identified to influence aesthetic preference such as luminance, contrast, complexity and novelty (Capo et al., 2008). There is no indication in Kawabata and Zeki's (2004) procedure about whether they controlled for these variables. Thus, although the pursuit of a brain basis for beauty is at least interesting, it is sadly plagued by confounds and methodological issues.

Conclusion

So, is there a single set of characteristics that defines beauty? According to Zeki and his colleagues: yes, there is. The mOFC is suggested to provide a brain basis for the perception of beauty. Unfortunately, Zeki's studies may rest too heavily on philosophising and, frankly, wishful thinking. Besides his ambitious hypotheses, elaborate explorations and flowery language, the numerous methodological considerations in his research provide ample room for scepticism about what he posits. This collection of concerns includes the issue of subjectivity, small sample sizes, and the lack of control conditions or variables. Taken together, while utterly alluring, Zeki's theory is currently just that: a subjectively-beautiful theory.

Psychedelics and the predictive mind: A review of the potential mechanisms that underpin the efficacy of psilocybin to treat depressive disorders.

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There has been a recent surge of scientific attention investigating the clinical effects of psilocybin, due to several promising lines of research demonstrating psilocybin's robust anxiolytic and antidepressant effects. However, the putative mechanism that underlies the therapeutic effects of psilocybin-assisted therapy (PAP) remains speculative (Swanson, 2018). Therefore, this literature review aimed to synthesise the key mechanisms that contribute to clinical improvement when using PAP to treat depressive disorders. In this literature review, a predictive processing framework will be used to (1) discuss the neurobiological effects of psilocybin, (2) highlight complex psychological changes and mystical/peak experiences typically associated with psilocybin, (3) present extra-pharmacological factors that are associated with clinical improvement in PAP, and (4) argue that the network theory of mental disorders (Borsboom, 2017) may be a useful tool for future clinical psychedelic research. We speculate that $5HT_{2A}R$ agonism may serve to reduce the precision of maladaptive high-level priors, which leaves a window of opportunity for psychotherapy. However, through the integration of evidence from a neurobiological and psychological standpoint, we argue that there are many other factors that mediate PAPs efficacy in treating depressive disorders.

1 - Introduction

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptami-ne) is a psychedelic drug that has received growing attention from the scientific community in the past twenty years. Psilocybin falls under the broad umbrella of substances dubbed classic psychedelics. These classic psychedelics are, by definition, full or partial $5HT_{2A}R$ agonists (Nichols, 2016), however this pharmacological mechanism of action can not explain the heterogeneity of effects between different classic psychedelic substances. Examples of other classic psychedelics are ayahuasca, which contains the psychoactive component dimethyltryptamine (DMT), lysergic acid diethylamide (LSD) and 3,4,5-trimethoxyphenethylamine (mescaline), the psychoactive component found in psychedelic cacti such as peyote.

Psilocybin has been used for centuries in a variety of religious and spiritual contexts. For example, the Aztecs often used psilocybe mushrooms, which contain the psychoactive component psilocybin, in religious healing ceremonies (Nichols, 2016). Moreover, psilocybin, as well as other classic psychedelics, have demonstrated themselves as efficacious treatments for a variety of mental health disorders, ranging from addiction and alcoholism (Krebs & Johansen, 2012) to existential distress in terminally ill patients (Thomas et al., 2017). Psilocybin-assisted psychotherapy (PAP) has demonstrated robust efficacy in treating depressive disorders in recent psychopharmacological trials (see section 3.1). However, there is an explanatory gap that needs to be addressed: we are yet to understand which effects of psilocybin (both in the brain and subjective experiences) facilitate clinical improvement (Swanson, 2018).

This literature review aims to address this fundamental question by synthesising recent evidence from cognitive neuroscience, psychology, and clinical neuroscience. Further to this, predictive processing will be used as a foundational framework for this review. The integration of predictive processing and psychopathology is a relatively recent endeavour in cognitive neuroscience. Therefore, this review contributes to the understanding of the interactions between models of predictive processing and psychopathology. Further to this, other reviews that attempt to underpin the efficacy of psychedelics to treat mental health issues view it through a purely neurobiological lens (Vollenweider & Kometer, 2010; Nichols et al., 2017). We, however, aim to provide a more interdisciplinary account, discussing neurobiological, psychological and extra-pharmacological factors that have demonstrably contributed to the clinical improvement of patients. We also aim to further conceptualise and understand depressive disorders through less reductionist means, namely by advising future researchers to use the network theory of mental disorders. By doing so, this may equip researchers to gather a more comprehensive understanding of both the neurobiological and psychological functioning of patients in future clinical trials using PAP.

It is important to mention here that the review question is solely focused on psilocybin's therapeutic effects. However, the pharmacological mechanism of $5HT_{2A}R$ agonism, which is seemingly responsible for the majority of psilocybin's hallmark effects (Vollenweider et al., 1998), is found in other classic psychedelics. Therefore, it could be argued that other classic psychedelics may be effective in treating the same mental health issues. However, since the turn of the century, there has been a larger ongoing research effort investigating the effects of psilocybin. Furthermore, the subjective effects of psilocybin have been found to be tolerable, with minimal unpleasant experiences when administered in a controlled setting, the most common of which is transient anxiety (e.g. Carhart-Harris et al., 2016a; Griffiths et al., 2016). Conversely, for example, the psychedelic ayahuasca often yields unpleasant subjective effects; many users experience intense nausea and vomiting (Shanon, 2002), which may prove difficult to integrate into Western therapeutic protocols. Therefore, due to psilocybin's tolerable effects and broad range of research, it seems fruitful to narrow the scope of the topic of this review solely to investigate the mechanisms that underpin psilocybin's efficacy in treating depressive disorders.

The structure of this review is as follows. Firstly, a brief introduction to predictive processing, the free energy principle, and hierarchical predictive coding will be presented. Predictive processing theories of depressive disorders will then be reviewed. These theories primarily argue that depressive disorders manifest due to over-precise maladaptive predictions (priors), which facilitates a depressive generative model of the world. This novel theoretical perspective will serve as the foundational framework of this literature review. Secondly, we will provide an overview of fundamental neurobiological and psychological studies using psilocybin, as well as modern trials that use PAP. Thirdly, extra-pharmacological factors that have a role in clinical improvement will be presented. Fourthly, key insights from meditation research will be explored. This pertains to the neurobiology and phenomenology of deep meditative states. It will also be argued that, over longer periods of time, there is a similar mechanism at play involved in a long-term meditation practice, namely that maladaptive over-precise priors are downweighted. Finally, we discuss the implications of using the network theory of mental disorders (Borsboom, 2017) in future research using PAP. A synthesis of evidence from these different facets of research can allow us to develop a deeper understanding of the clinical effects of PAP.

2 - Predictive Processing

2.1 Introduction to the Free-Energy Principle

According to the free energy principle, the brain, and other biological systems, are allostatic. In order to maintain homeostasis the brain aims to minimise average surprise over time - formally measured as entropy (Friston, 2010). Average surprise over time is underpinned neurobiologically by prediction errors, where there is a mismatch between the brain's generative model of the world (top-down predictions) and received information (bottom-up sensory input). In order to reduce surprise (or entropy) the brain acts as a Bayesian inference machine, actively comparing prior beliefs about the world with data, and updating posterior beliefs about the world dependent on the mismatch between the generative model and the likelihood of the data (Friston et al., 2006).

The brain may minimise the accumulation of prediction errors in two ways. Firstly, if there is a mismatch between the brain's generative model and incoming sensory data, then the brain can update its generative model. Thereby, the predictions made by the generative model more accurately reflect the incoming bottom up sensory information, which subsequently minimises prediction errors (Knill & Pouget, 2004; Huang & Rao, 2011; Kanai et al., 2015). For example, an individual may predict that there is a large amount of water in a nearby opaque water bottle, thus believing it is heavy. In reality, there is a small volume of water in the bottle, rendering it light. When that individual picks the bottle up, they exert an unnecessary amount of force. This leads to a prediction error, as there is a mismatch between the incoming sensory information and the top down predictions. In order to minimise this prediction error, the prediction is updated from "The bottle of water is heavy" to "The bottle of water is light". The brain can also minimise the average surprise through another route known as active inference (Friston et al., 2016); the brain will change its actions in concordance with its generative model. In a separate example, an individual may not be able to see well on a foggy day. On this foggy day they see a shape in the distance, but, due to unreliable sensory signals, they are not able to clearly discern what the shape actually is. In this instance, the individual employs the strategy of active inference, by moving towards the shape in order to discern what it actually is.

2.2 Hierarchical Predictive Coding

A fundamental component of the free-energy principle is that the brain is composed of a hierarchy. Classic neuroscientific research has elucidated that the brain is structurally composed of a hierarchical set of regions (Felleman & Van Essen, 1991; Dombrowski et al., 2001; Vezoli et al., 2004). Regions at the top of the hierarchy, such as prefrontal cortical regions, will process multimodal information, and thus encode probabilistic representations of the sensorium. Regions at the bottom of the hierarchy (e.g. early visual cortical areas) send sensory information up the hierarchy via feedforward connections. The top-down predictions are formally encoded by deep layer pyramidal cells (Bastos et al., 2012), whereas the bottom up sensory information is propagated via superficial layers in the cortical hierarchy.

Further to the fact that probabilistic representations need to be encoded in order to minimise the surprise, the brain also needs to assign a certain amount of precision to the predictions that comprise the generative models. Precision-weighting in a predictive coding model is required as it allows the brain to downweight noisy sensory information, or upweight sensory information in unfamiliar situations. However, this precision-weighting mechanism may become problematic when the predictions are over-precise. When

conceptualised as a probability distribution, the precision is the inverse variance of the distribution. When sensory information is assigned with excessive precision, sensory input will dominate perception (Lawson et al., 2014). Conversely, when a prior belief is overly precise, there needs to be a great deal of prediction error in order to update the generative model in alignment with the incoming information. Therefore, when prior beliefs are assigned with excessive precision, the prediction errors that discount them are down-weighted.

As prediction errors are a representation of the mismatch between the brain's generative model of the world and the incoming sensory information, prediction errors serve as the basis for updating the brain's generative model. However, over-precise priors will result in over-confidence in the generative model. This is due to the fact that the prediction errors are downweighted, culminating in predictions that are resistant to incoming sensory evidence (Bruineberg et al., 2016). Incorporating this concept of stubborn predictions may be informative for cognitive theories, and yield more explanatory power (Yon et al., 2019). For example, when over-precise predictions are maladaptive, they have widespread implications for the development of psychopathologies, as will be explored below.

2.3 Predictive Processing & Depressive Disorders

Predictive processing has proven particularly useful in modern cognitive neuroscience. It has been used to explain various phenomena (for perception, see Friston, 2005; emotion, see Seth, 2013; for action, Friston, 2003; Friston et al., 2011; and for thought, Metzinger, 2017). Moreover, the predictive processing framework has been useful to explain how mental health disorders may manifest and sustain themselves. In this section, we will explore various predictive processing theories of depressive disorders, highlight the common theme of over-precise maladaptive priors, and introduce neurobiological evidence for the role of over-precise priors.

Chekroud (2015) used the free energy principle to hypothesise that depression may emerge in individuals from a constellation of depressive beliefs. These depressive beliefs (conceptualised as probability distributions) then serve to negatively bias the predictions that the brain makes, which ultimately manifests in cardinal symptoms of major depressive disorder (MDD) such as low mood and anhedonia. Chekroud (2015) argues that there may be various neuromodulatory systems that facilitate these depressive beliefs, but unifying treatments of MDD may be achieved through the longitudinal updating of these maladaptive priors to healthier ones. Other researchers characterise the emergence of the depressive phenotype through abnormally precise priors (Clark et al., 2018; Edwards et al., 2012; Kube et al., 2019). As previously stated, assigning too much precision to priors will lead to an inability to update the generative model. If these abnormally precise priors are maladaptive, then any incoming prediction error, due to a mismatch between high level beliefs and discounting sensory information, will be down-weighted and will subsequently not lead to an update in the generative model. Kube et al. (2019) further argues that prefrontal cortical regions have a mediatory role in this process, as they can impose these top down aberrant predictions on lower levels of the hierarchy, such as the ventral striatum, a region responsible for reward processing (Berridge & Robinson, 1998).

High level priors are thought to be encoded by cortical areas at the top of a deep seated hierarchy of the brain (Carhart-Harris & Friston, 2010; Park & Friston, 2013). One such network that has captured the attention of cognitive and clinical neuroscience is the Default Mode Network (DMN; Raichle et al., 2001). The DMN is a network of a group of midline cortical areas that are functionally and structurally connected with each other (Greicius et al., 2009; van den Heuvel et al., 2008). The DMN shows demonstrable anti correlation with the task positive network (TPN), an attention network associated with goal directed cognition (Fox et al., 2005). Carhart-Harris & Friston (2010) argue that the DMN serves to suppress the signalling of prediction errors (i.e. free energy) through the use of top-down predictions. Strikingly, the DMN has been implicated in a variety of psychopathologies (Broyd et al., 2009; Simon & Engström, 2015). A lack of anticorrelation between the DMN and TPN has been associated with major depression (Sheline et al., 2009), and abnormal functional connectivity is associated with the intensity of depressive rumination (Berman et al., 2011) and severity of symptoms (Greicius et al., 2007). Moreover, the DMN has been implicated in self-reflective thought (Gusnard et al., 2001; Sheline et al., 2009), which may point to the idea that the DMN represents high level priors relating to the self. Overactivity in the DMN has also been implicated in MDD patients during passive observation and active reappraisal of negative pictures (Sheline et al., 2009). All of these findings align with the hypothesis proposed in a predictive processing frame of depressive disorders, as an overactive DMN may be a neurobiological correlate of over-precise maladaptive priors. It is noteworthy that, if priors are to facilitate a depressive generative model of the world, these over-precise priors are maladaptive. An inability to suppress these maladaptive priors, due to the excessive precision assigned to them, leads to hallmarks of depressive cognition such as depressive rumination (Nolen-Hoeksema, 2000) and attentional biases for negative information (Donaldson et al., 2007).

The prospect that regions higher in the hierarchy inhibit the processing of prediction errors to facilitate a generative depressive model of the world is intriguing. This prospect may explain why there is a discrepancy in the literature between emotional reactivity and hedonic pleasure. For example, it has been found that there was not a blunting in hedonic response to sweet tastes in MDD (Berlin et al., 1998; Dichter et al., 2010). However, emotional reactivity when processing more complex stimuli, such as facial expressions, films and music, is reliably blunted in MDD (Bylsma et al., 2008). These more complex stimuli require processing from high level multimodal areas such as those in the DMN, whereas hedonic response to primary rewards such as pleasure from sweet tastes are less reliant on these multimodal areas. This points to the idea that over-precise depressive priors are more likely to have an

influence in the way that complex multimodal stimuli, such as facial expressions, films and music, are processed and appraised.

2.4 Interim Summary

Predictive processing is a unifying framework in cognitive neuroscience that has managed to explain a vast array of phenomena since its conception. An increasing body of work in the last several years has focused on how psychopathologies may develop, with particular regards to depressive disorders. The mechanism in question that is frequently cited in predictive processing theories of depressive disorders is an overconfidence in maladaptive beliefs, encoded through over-precise priors. It is argued that these high-level priors are held in areas believed to sit at the top of the hierarchical structure of the brain, such as the DMN. As the DMN has widespread implications for the functioning of the rest of the hierarchy, these maladaptive priors may facilitate the emergence of depressive disorders. This is due to the fact that prediction errors between incoming sensory signals and the maladaptive priors are downweighted due to the over-precise nature of said priors, leading to the manifestation and maintenance of a depressive generative model of the world that fails to update due to the stubborn predictions (Yon et al., 2019).

3 - Psilocybin

In this section we lay a foundation that explains the general pharmacology of psilocybin, neuroimaging studies that detail its neurobiological effects, the psychological effects of psilocybin, and studies that have found PAP to be an efficacious treatment for a variety of mental health disorders.

3.1 Recent Clinical Psychopharmacological Studies Using Psilocybin

Here we begin by reviewing the empirical studies that have investigated the effect of PAP on mental health disorders. The first modern psychopharmacological study that investigated the effect of psilocybin on cancer related mental health was a double-blind, placebo-controlled (niacin) study that used a moderate dose (0.2mg/kg oral) (Grob et al., 2011). The study conducted was a pilot designed to explore the safety of psilocybin in advanced-stage cancer patients, and thus the sample was relatively small with twelve patients with advanced-stage cancer and a DSM-IV diagnosis of acute stress disorder, generalised anxiety disorder, anxiety disorder due to cancer or adjustment disorder with anxiety. The Beck Depression Inventory (BDI) was used as a primary depression measures, while the State-Trait Anxiety Inventory (STAI) was used as a primary anxiety measure. The results showed that there were no significant adverse responses to psilocybin, which was the primary investigation of the study. There was a nonsignificant reduction in BDI scores ($p=0.08$) until the 6-month follow-up point ($p=0.03$). Reduction in STAI trait anxiety, however, reached significance at the 1-month ($p=0.001$) and 3-month ($p=0.03$) time points, compared to baseline.

Following on from the findings of this study, (Griffiths et al., 2016) investigated the effects of a high dose (22 or 30mg/70 kg) of psilocybin on various measures of depression (BDI, Hamilton Depression Rating Scale (GRID-HAMD-17), Hospital Anxiety and Depression Scale (HADS) and anxiety (Hamilton Anxiety Rating Scale (HAM-A), STAI). The final sample consisted of 51 patients with a potentially life threatening cancer diagnosis and a range of DSM-IV mood disorder diagnoses (see table 1 for details). The study used a double-blind cross-over design, which compared a high dose of psilocybin with a very low dose (1 or 3mg/70 kg), with the conditions 5-weeks apart. Results showed that, for patients that experienced the high dose first, there were significant clinical improvements on the GRID-HAMD-17 ($p<0.001$), BDI ($p<0.01$), HAM-A ($p<0.001$), HADS ($p<0.05$) and STAI ($p<0.05$) before the cross-over to the low dose. Further to this, approximately 80% of patients maintained a clinically significant reduction in depression and anxiety at a 6-month follow up.

Another study investigated the effects of psilocybin on cancer-related depression and anxiety using the same double-blind, placebo-controlled, crossover design, with 29 patients with life-threatening cancer (Ross et al., 2016). A single psilocybin dosing session (0.3mg/kg) was crossed over with a placebo session (niacin), with approximately 7 weeks between each session. Preparatory and Another integrative psychotherapy was also administered to all participants, in order to maximise the potential clinical benefits of the dosing session(s). Similar to Griffiths et al. (2016), there was a significant reduction in depression and anxiety for patients that received psilocybin in the first session, compared to patients that received a placebo. At a 6.5 month follow up (after both sessions) approximately 60-80% of patients displayed clinically significant reductions in depression and anxiety on a variety of measures.

Psilocybin has also demonstrated its efficacy outside the realms of cancer-related depression and anxiety. Carhart-Harris et al. (2016a) recently conducted an open-label pilot study that investigated the effects of PAP on patients with treatment-resistant major depression (TRD). The sample consisted of 12 patients with severe major depression. The illness had lasted for an average of 18 years, and had been unresponsive to both medication and various forms of psychotherapy. Patients received a low to moderate dose of psilocybin (10mg/70kg) on the first session, and then a high dose (25mg/70kg) on the second session, one week apart. One week after the high dose session there was a significant reduction on the Quick Inventory of Depressive Symptoms (QIDS) ($p=0.002$; Hedges' g[1] = 3.1), BDI ($p=0.002$; Hedges' g = 3.2), and HAM-D ($p=0.003$; Hedges' g =2.4). These significant reductions endured at the 3-month follow-up for QIDS ($p=0.003$; Hedges' g = 2.0) and BDI ($p=0.002$; Hedges' g = 2.0). HAM-D was not tested at the 3-month follow-up as it was a clinician-administered rating. Carhart-Harris et al. (2018) also reported an extension of the aforementioned study, with eight new patients included in the analysis, and a six-month time point included. The QIDS score was significantly reduced at every time point ($p<0.001$) with the effect

1 Hedges' g was used as it is more appropriate for small sample sizes.

size largest at 5-weeks post treatment (Cohen's d = 2.3). The effect size remained large at the 6-month follow-up (Cohen's d = 1.6) and there was a significant reduction in BDI scores ($p<0.001$) and QIDS-SR16 scores at all time points, including the 6-month mark.

3.2 Psychopharmacology

These recent clinical psychopharmacological studies have demonstrated how PAP may serve as an efficacious and long-lasting treatment to increase the quality of life in patients with terminal cancer, and also as a treatment for patients with TRD. To understand the extensive effects of psilocybin on the brain, here we will briefly summarise the psychopharmacology of psilocybin.

Psilocybin is an indolealkylamine (Passie et al., 2002) - a chemical derivative of 5-hydroxytryptamine (5-HT or serotonin). Psilocybin has a strong affinity for the receptor subtype 5-HT_{2A}R, but also has binding potential for many other 5-HT receptor subtypes, and dopamine (Ray, 2010). Although the pharmacodynamics of psilocybin are far-reaching and not fully understood, there has been extensive research that posits 5-HT_{2A}R agonism as the underlying neurobiological mechanism that is responsible for the majority of psilocybin's, and other psychedelics (Halberstadt, 2015), hallmark effects[2]. Administration of ketanserin, a 5-HT_{2A}R antagonist, prior to the administration of psilocybin completely attenuated self reported intensity of the drug, as measured by the 5-Dimensional Altered States of Consciousness rating scale (5D-ASC) (Quednow et al., 2012), reversed psilocybin-induced positive mood (Kometer et al., 2012), and prevented the psychotomimetic effects of psilocybin (Vollenweider et al., 1998).

5-HT_{2A}Rs are most abundantly expressed in the cortex (Varnäs et al., 2004), particularly in high-level associative cortex (Beliveau et al., 2017), where many regions belonging to the DMN (Raichle et al., 2001) are located. Psilocybin induces cortical excitability through the activation of 5-HT_{2A}Rs on excitatory glutamatergic pyramidal neurons in layer V of the cortex (Weber and Andrade, 2010). This is particularly important, as within the predictive processing framework, these neurons sit at the top of a deep seated hierarchy within the brain, and, as stated in section 2.2, are thought to encode prior expectations and beliefs in a predictive processing framework (Bastos et al., 2012).

3.3 Neuroimaging Studies and Psilocybin - Top Down Disinhibition

There have been a variety of neuroimaging studies that have attempted to elucidate the widespread effects of psilocybin on the human brain. Many of these studies have integrated network approaches to investigate how whole brain dynamics can be influenced by psilocybin. These studies reveal changes to functional connectivity and effective connectivity as a result of psilocybin administration. In this section, it will be argued that psilocybin primarily exerts its effects through the disinhibition of top down networks, which allows a reduction in biased rigid hierarchical processing. This, we contend, may be critical in explaining its antidepressant and anxiolytic effects.

Research has found that intravenously-administered psilocybin can reduce the blood-oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) signal in regions belonging to the default mode network such as the posterior cingulate cortex (PCC), the anterior cingulate cortex (ACC), and the medial prefrontal cortex (mPFC) (Carhart-Harris et al., 2012). The benefit of intravenous administration of the drug is that it has a much smaller duration of subjective effects on the participant (approximately 45-60 minutes), and is therefore ideal for neuroimaging studies. Carhart-Harris et al. (2012) also found that the greater the decrease in cerebral blood flow, the more intense the effects of psilocybin (as measured on the 5D-ASC). As a possible alternative explanation, the researchers hypothesised that these changes in CBF were due to the potential hypercapnic effects of psilocybin - where psilocybin-induced vasodilation elevated CO2 - thus affecting the BOLD signal. However, this critique was dismissed, as they found no difference between the effects of a breath-hold task in both the psilocybin and the placebo condition. Moreover, the decrease in activity in maximal hub regions has been corroborated in other studies, further strengthening the case against a psilocybin-induced vasodilation mechanism. Muthukumaraswamy et al. (2013) used dynamic causal modelling (DCM) and magnetoencephalography (MEG) with participants that had been intravenously administered psilocybin. They found there was a general broadband desynchronisation of cortical oscillatory rhythms, and these were primarily localised to marked decreases in the DMN. DCM was used to uncover the most likely synaptic mechanism that underlies the observed broadband desynchronisation (the data used was spectral decreases in the PCC). It was found that excitation of deep layer pyramidal cells were the most likely candidate for the spectral decrease in the PCC. DCM was also used in another BOLD fMRI experiment that found an attenuation of amygdala reactivity to negative and neutral stimuli after administration of psilocybin (compared to placebo) (Kraehenmann et al., 2015). The marked decrease in amygdala activity contributes to the potential neurobiological mechanisms that may underpin depressed mood, as hyperactivity in the amygdala in fearful emotional processing has been found in patients with major depression (Sheline et al., 2001), and the reduction in amygdala response correlated with the psilocybin-induced increase in positive affect. DCM revealed that the modulation of top down connectivity from the amygdala to the visual cortical area V1 decreased after psilocybin administration (Kraehenmann et al., 2016). Both Muthukumaraswamy et al. (2013) and Kraehenmann et al. (2016) corroborate with evidence that demonstrates that the net effects of deep layer pyramidal cells is inhibitory (Bastos et al., 2012), and would therefore suitably explain the decrease in oscillatory power in high level regions, and a reduction in activity in the amygdala and V1.

In systems level neuroscience, there is partial overlap between rich clubs, highly interconnected to the rest of the network of the brain, and the DMN (Sporns, 2014; van den Heuvel & Sporns, 2011). It can therefore be hypothesised that, after the administration of psilocybin, there are widespread changes throughout the whole of the network of the brain. Predictably, these effects have been found

in psychedelic research. As well as general broadband decreases in spectral power, and decreased activity in maximal hub regions, it has also been found that psilocybin can disturb/disintegrate the functional connectivity of brain networks. For example, Roseman et al. (2014) found a large number of resting state functional connectivity (RSFC) networks that were significantly more coupled after psilocybin administration. Further to this, MDMA, which does not primarily act on 5-HT_{2A}Rs, only significantly increased the coupling of one pairing of RSFC networks. Petri et al. (2014) also found that psilocybin administration disrupted hallmark functional connectivity motifs, and significantly elevated the amount of homological scaffolds during the psychedelic state.

3.4 The Entropic Brain Hypothesis and REBUS and the Anarchic Brain

The neurobiological mechanisms that have been highlighted indicate that 5-HT_{2A}R agonism, particularly on layer V pyramidal neurons in high level associative cortex, may be responsible for three key neurobiological features. Namely, the disruption of typical resting state networks, the decrease in activity in maximal hub regions (both in spectral power and broadband activity), and attenuated amygdala reactivity in response to threatening stimuli. The former two features of the psychedelic state have been used as empirical evidence in a theory of conscious states (Entropic Brain Theory; EBT; Carhart-Harris, 2018; Carhart-Harris et al., 2014), and a unifying theory of psychedelic action (REBUS and the Anarchic Brain; Carhart-Harris & Friston, 2019). In this section, both of these theories will be documented, as they argue that the neurobiological action of 5-HT_{2A}R agonism is responsible for psilocybin's anxiolytic and antidepressant effects.

The EBT is a unifying theory of conscious states that uses predictive processing to argue that psychedelics primarily increase the order of entropy in the brain. Entropy is a dimensionless quantity that serves as a measure of uncertainty in the brain. As has been discussed in section 2.1, in a predictive processing framework, entropy is synonymous with free energy. The brain's primary task is to minimise this free energy (Friston, 2010). In the EBT, conscious states lie on a spectrum; on the one side, you have low entropy states of extreme cognitive rigidity and inflexibility, which comprise of mental health disorders such as depression, obsessive compulsive disorder, and addiction. On the other end of the entropic scale, you have high entropy states, characterised by unconstrained cognition. Exemplary high entropy states are the psychedelic state, early psychosis, and deep meditative states. The authors further hypothesise that, due to 5-HT_{2A}R agonism primarily in layer V pyramidal neurons in high level associative cortex, psychedelics such as psilocybin increase the entropy of the brain. Thus, this increases the flexibility of cognition and has implications for metacognitive functions. The authors argue that the therapeutic benefits of psychedelics lie in this mechanism - of increasing entropy within the brain.

The REBUS model (Carhart-Harris & Friston, 2019) extends the EBT, and presents a unifying theory of the action of psychedelics. Within this theory, the authors argue that specifically high level priors are made more flexible through psychedelic use, as exemplified through the deactivation of high level cortical regions (Carhart-Harris et al., 2012), which leads to a disinhibitory effect on the rest of the brain (Petri et al., 2014; Roseman et al., 2014). The authors also argue that many psychopathologies emerge from entrenched negative thought patterns that become increasingly difficult to break. It is therefore argued that, due to the relaxation of these high level priors, psychedelics, such as psilocybin, have the potential to provide some flexibility to these negative thought patterns that perpetuate specific mental health disorders.

Despite the mounting evidence that supports the idea that psilocybin and other psychedelics exert their effects through increased entropy in the brain (e.g. Lebedev et al., 2016; Muthukumaraswamy et al., 2013; Schartner et al., 2017; Viol et al., 2017) there are several reservations that must be stated. Firstly, entropy measures are receiving an increased amount of attention in the field of cognitive neuroscience, and, like many emerging methods, they suffer from heterogenous research practices. The heterogeneous research practices primarily stem from differing neurophysiological and methodological measures of entropy. For example, Carhart-Harris et al. (2014) formally use Shannon entropy as a measure of uncertainty. However, there are many other methods that are used to measure the entropy of a system. If research is to continue using entropic measures there needs to be a concerted effort to adopt a standardised procedure, so that findings can be compared and contrasted with increased validity. Secondly, there are mixed results in the literature that uses entropy as a measure when contrasting patients with major depressive disorder (MDD) and typical healthy controls. Some research has found decreased entropy in MDD patients compared to healthy controls (Pezard et al., 1996; Xue et al., 2019). Whereas other research has found contrary results; MDD patients had heightened entropy, both globally (Li et al., 2008) and in anterior brain regions (Méndez et al., 2012), compared to healthy controls. The discrepancy between these results in mental health research could be due to the fact that the use of entropy as a measure of uncertainty in the brain is subject to a variety of external influences. Potential external factors that may influence the results of this are the notable heterogeneity of MDD and other mood disorders, and the varying definitions of entropy, complexity and neurophysiological measures used in each study. Future researchers that investigate the entropic state of patients with mental health disorders may find it useful to conduct more longitudinal analyses of entropy in patients. Longitudinal studies may help to navigate the confounding effect of context and transient mental states, permit comparisons of state entropy to trait entropy, and reveal differences in the fluctuations of entropy within individuals (and across disorders) over time.

Despite these shortcomings, the neurobiological findings in psychedelic studies are mounting which increasingly support the EBT hypothesis that entropy is heightened in the psychedelic state. As entropy is synonymous with free energy (or prediction errors) in the brain, this further supports the idea that psilocybin, and other psychedelics, may disinhibit the top down predictions that are propagated by high level hierarchical regions such as the

DMN. The EBT and REBUS models both cite this entropic action as the potential mechanism that underpins the therapeutic utility of psilocybin and other psychedelics. However, in clinical studies that use PAP, the quality of the psychedelic experience mediated the therapeutic outcomes of the PAP (Griffiths et al., 2016; Ross et al., 2016; Carhart-Harris et al., 2018). In the following section, we outline possible first-person and phenomenological aspects of the psychedelic experience that may play a key role in therapeutic outcomes.

3.5 Psilocybin Occasioned Mystical/Peak Experiences

Due to the extensive work conducted in investigating how the quality of the psychedelic experience can contribute to complex psychological changes, it is important to explore these variables in the therapeutic process. It may be excessively reductionist to explain away the clinical efficacy of psilocybin solely due to a pharmacologically-induced mechanism. Therefore, it is important for researchers to carefully consider and potentially facilitate positive psychedelic experiences (discussed further in the context of set and setting in section 4.1). Here we will explore how specific psilocybin-induced experiences can lead to psychological changes, and argue that these ultimately contribute to the therapeutic outcome.

Many psychologists have been intrigued by the idea that a profound subjective experience can lead to enduring psychological changes (Miller, 2004). However, research has only been able to study these changes in a correlational setting (e.g. Costa et al., 2000; Mroczek & Spiro, 2003). This has left researchers unable to infer causality between specific life events and the complex psychological changes that may subsequently occur. However, since the turn of the century, psilocybin has provided many researchers with the unique opportunity to investigate how a single experience can affect the psychology of a participant in a controlled laboratory setting. (MacLean et al., 2011) found that, when administered to hallucinogen-naive participants in a controlled setting, a high dose (30mg/70kg) of psilocybin significantly increased measures of Openness (which encompasses aesthetic appreciation, a vivid imagination, and a large tolerance of individuals' values and views). These effects were mediated by the presence of a complete mystical experience (Stace, 1960). For participants that underwent a complete mystical experience, the increase in Openness remained significant at a 16-month follow-up. Further to this, Griffiths et al. (2011) found that psilocybin significantly increased positive attitudes about life, the self, mood, and behaviour, and these positive changes monotonically increased as the dose of psilocybin increased. Again, the authors ascribe these positive changes to participants having a complete mystical experience. Notably, the percentage of participants that had a mystical experience also increased as a function of dose. Griffiths et al. (2008) similarly found that mystical experiences mediated whether participants appraised the psilocybin experience with personal meaning and spiritual significance. Extending this to a clinical population, research using a PAP protocol found that mystical-type experiences under a high dose of psilocybin mediated its anxiolytic and antidepressant effects (Griffiths et al., 2016; Ross et al., 2016; Carhart-Harris et al., 2018), and high measures of Oceanic Boundlessness - linked to the original definition of "mystical-type" experiences (Stace, 1960) - during the psychedelic experience predicted clinical improvement in depressive symptoms (Roseman et al., 2018).

Due to these apparent mediatory effects of mystical experiences, it is therefore necessary to define what constitutes a mystical experience. Mystical and spiritual experiences are classically defined as when an individual loses their sense of space and time, feels a strong connectedness with the external environment, loses the awareness of their physical self, and has a deep felt sense of peace and joy (Stace, 1960). In a predictive processing framework, mystical and spiritual experiences are hypothesised to arise due to interoceptive and exteroceptive signals becoming differentially weighted (van Elk & Aleman, 2017). In this differential weighting, exteroceptive signals may be upweighted, which leads to a downregulation of one's sense of self, which may explain the perception that an individual is more connected to the external environment during such an experience. Further to this, altered DMN activity has been implicated in drug induced ego dissolution (DIED; Lebedev et al., 2015), a phenomenon that is characteristically similar to the mystical experience.

Although the neurobiological mechanisms that underpin a mystical experience, or DIED, are unclear, these profound experiences have been documented to aid in the improvement of psychological well-being, whether influenced by psilocybin (Maclean et al., 2012; Griffiths et al., 2016; Ross et al., 2016; Roseman et al., 2018), or through other means (Ludwig, 1985; Snell & Simmonds, 2015; Trigwell et al., 2014). Therefore, it may be useful to explain why these experiences are so beneficial in a therapeutic context. In a predictive processing framework, these profound mystical-spiritual type experiences may influence the brain's generative model. The differential weighting between interoceptive and exteroceptive signals, as a result of a mystical-spiritual experience, may lead to an update of the generative model, so that the individual then reweights exteroceptive signals over interoceptive signals (van Elk & Aleman, 2017). By doing so, interoceptive signals that may facilitate the depressive generative model of the world (such as depressive rumination) may be downweighted, which can lead to exteroceptive signals having more influence on the brain's generative model. If these subsequent exteroceptive signals are positive, this can lead to a positive model update, and ultimately to clinical improvement.

It is noteworthy here, however, that the construct of a mystical experience suffers from heterogeneity of practices and definitions. It seems that there is an overlap between different constructs that are used - DIED, mystical and spiritual experiences - and there are different questionnaires employed. For mystical experiences, there is the Mystical Experience Questionnaire (MEQ) (Pahnke, 1969) and the Hood Mysticism Scale (Hood et al., 1993; Hood, 1975). The MEQ30 (Maclean et al., 2012), made of a subset of thirty questions from the MEQ, has been confirmed to have good internal

reliability and convergent validity in an online survey sample (Maclean et al., 2012) and in an experimental setting (Barrett et al., 2015) for participants that have had a psilocybin-induced mystical experience. DIED, however, is measured through the Ego-Dissolution Inventory (EDI), which has demonstrable convergent validity with the MEQ (Nour et al., 2016), and directly relates to the dissolution of the sense of self, space and time, which all map onto the original definition of a mystical/spiritual experience. Roseman et al. (2018) used a principal Altered States of Consciousness (ASC) factor, Oceanic Boundlessness (OBN), which has its roots in Freudian psychology (Freud, 1920) and has a conceptual overlap with the original definition of mystical experiences by Stace (1960). The researchers found that the magnitude of OBN during the psilocybin experience mediated the positive clinical outcomes in a PAP study for TRD. Measures of psychedelic-induced mystical or spiritual type experiences have recently been moving towards more secular definitions and constructs (such as DIED and also "peak experiences", a term coined by Maslow, 1962), as some researchers wish not to endorse the metaphysical ideas that may be implicitly associated with mystical experiences, so they may be scrutinised within the standard scientific process (Carhart-Harris & Goodwin, 2017; Roseman et al., 2018).

4 -Extra Pharmacological Factors

External factors not purely related to the psychopharmacological mechanisms of psilocybin will be discussed here.

4.1 Set and setting

Following on from the potential psycho-spiritual mechanisms that underpin PAPs effectiveness to treat mental health conditions, it is important to note the necessity of the set and setting in which PAP is administered. The concept of set and setting emerged in the psychedelic literature in the 1960's (Leary et al., 1963), and was a term used to describe two crucial factors that often shape the psychedelic experience. Set refers to the expectations, mood, personality and intention of a participant, whereas setting refers to the environmental context in which a psychedelic is administered (Hartogsohn, 2017). In therapeutic applications of classic psychedelics, both set and setting were found to be crucial variables; using a positive set and setting within the psychedelic experience would often lead to enhanced clinical outcomes (Krebs & Johansen, 2012; Rucker et al., 2016). Conversely, if the set and setting were ignored, or even constructed in a negative manner, the therapeutic effects of PAP were comparably weaker (Ludwig et al., 1969; Oram, 2014). This illustrates the importance of variables such as mood state before administration, expectations of the experience, intention, and the environmental setting where PAP is administered.

Since the renaissance of psychedelic science at the turn of the century, most modern studies have learnt from the mistakes of the 1950's and 1960's; participants are thoroughly screened and prepared for the experience, the drug is administered in a calm environment with low lighting, and a carefully curated playlist of music is often played. Kaelen et al. (2018) found, through semi-structured interviews, that positive experiences with the music during PAP was associated with mystical experiences (as defined in section 3.5). Further to this, reductions in depressive symptoms one week after PAP were predicted by the nature of the music experience, but crucially not by drug intensity. Other research identified and classified different types of music that can more readily facilitate "peak experiences" of a psilocybin session (Barrett et al., 2017). As demonstrated before, there is a mediatory role of these mystical and peak experiences in the therapeutic model of PAP. Therefore, it should be of crucial importance to curate and employ the most therapeutically conducive environment during the PAP sessions. By doing so, researchers can more readily facilitate these psycho-spiritual phenomena in patients, which may translate into more clinical improvement.

Despite the fact that psilocybin is considered one of the least harmful illicit substances (Nutt et al., 2010), the context should also be paid attention to as there are cases in which psychedelic use can cause harm. If, theoretically, psilocybin pharmacologically induces a relaxation of prior beliefs in participants, sensitivity to external signals will subsequently increase. If this sensory information is negative, such as a harsh and unsuitable environment, this may have a negative effect on the psychedelic experience. As addressed above, the quality of the psychedelic experience is crucial in shaping clinical outcomes, which may be due to a failure to reorganise priors, or even the reorganisation of maladaptive and clinically counterproductive ones.

To exemplify, one could consider a clinical trial using psilocybin that forgoes any therapeutic guidance. Further to this, the trial also uses a harsh environment with music that is not conducive to a positive clinical outcome. The psychedelic experience is subsequently shaped by these factors, which could result in heightened levels of anxiety. Transient anxiety is commonplace during a psychedelic experience in clinical trials, but is easily managed by the therapists present (e.g. Griffiths et al., 2016). However, as there is no therapeutic guidance, these feelings of discomfort and anxiety are pervasive throughout the dosing session. Not only does this specific context fail to facilitate a mystical-spiritual/peak experience, it also imbues the dosing session with psychological discomfort. Thus, maladaptive over-precise priors are not positively readjusted, they are negatively readjusted, due to the unpleasant incoming sensory information, resulting in a lack of clinical improvement.

In sum, clinical improvement is inextricably linked to factors such as expectation setting, mood, and the environment of administration. Therefore, it is important for future researchers to consider the factors that may facilitate clinical improvement in order to maximise the efficacy of psychedelic interventions. However, it is out of the scope of this review to discuss the specific settings that facilitate the most therapeutically beneficial psychedelic experiences (for a comprehensive historical review of set and setting, see Hartogsohn, 2017).

4.2 The Potential Role of Placebo

Another extra pharmacological factor to consider in PAP is the placebo response. The placebo response is thought to primarily be driven by the participants' expectation to improve (Stewart-Williams, 2004), and has a major effect in a variety of clinical trials. In a meta-analysis, Khan et al. (2012) analysed 115 trials investigating a variety of treatments for depression, and found that the placebo response accounted for 30-40% of the mean percentage symptom reduction in all trials (Khan & Brown, 2015).

(Hartogsohn, 2018; 2016) hypothesises that classic psychedelics may act as a super-placebo, due to a number of factors that are integrated in the experimental control of set and setting. As addressed section 4.1, expectations, the environmental context and positive clinician-patient relationships are several factors that comprise the set and setting (Hartogsohn, 2017). These factors are notably responsible for facilitating the placebo response. For example, high expectations of antidepressant medication effectiveness predicted a higher placebo response (Leuchter et al., 2014), and prolonged interaction with the specialist carrying out sham acupuncture enhanced the treatment response rates from 44% to 62% (Kaptchuk et al., 2008). This evidence, coupled with evidence that classic psychedelics can increase the suggestibility of participants (Carhart-Harris et al., 2015) has led to the idea that the clinical efficacy of PAP may be heavily driven by the placebo response. This idea is intriguing, as psychedelic research has been blighted by a lack of effective placebo-controlled studies, as psilocybin and other classics psychedelics produce profound subjective effects that are almost impossible to replicate in a placebo-controlled fashion. For example, Carhart-Harris et al.'s (2016a) study was open-label, which meant that all patients received an active dose of psilocybin on both occasions, and both the patients and the researchers were aware of this. It is therefore more difficult to rule out the placebo effect within this study. Further to this, even when studies do use a double-blind placebo controlled procedure in a clinical setting, there are still difficulties involved regarding the dismissal of placebo and expectancy effects. The main difficulty that researchers encounter when conducting psilocybin studies is that patients and clinicians are able to guess which session is placebo or psilocybin with high degrees of accuracy. This then can facilitate expectancy effects due to the clinicians and patients easily discerning the substances.

In the context of predictive processing, psilocybin may increase the flexibility of beliefs. In a clinical setting, this effect may also make the patient more open to the influence of expectation, and thus placebo. Therefore, this may indicate that the placebo effect may in fact be a mechanism through which psilocybin occasions changes in rigid beliefs and maladaptive priors. Hendrie and Pickles (2016) argue that placebo-like expectancy effects could serve to explain the results of Carhart-Harris et al.'s (2016a) PAP study on TRD; they stated that the percentage of the cohort that remained in remission three months after treatment (42%) roughly matches the figures that account for the placebo response in antidepressant trials (Khan & Brown, 2015). However, Carhart-Harris & Nutt (2016) rebutted to argue that their claims were overstated for three reasons. Firstly, Khan & Brown (2015) never mention remission rates in their literature review, only percentage of symptom reductions (30-40%). Secondly, if the results of Carhart-Harris et al.'s (2016a) study could be accounted for purely by placebo-like expectancy effects, then these results would be most pronounced at one week post 25mg PAP session. However, at one week post high dose PAP, there was a 74% reduction of BDI symptoms, which is a much higher percentage rate than Khan & Brown (2015) presented. Finally, the cohort of patients in the psilocybin trial were exceptional patients; they all had treatment-resistant depression for an average of eighteen years, and had not responded to a variety of pharmacological and psychological interventions. Therefore, it would be hasty to conclude that the recent clinical evidence supporting PAPs efficacy in treating depressive disorders is solely driven by the placebo response.

However, the placebo effect has proven to be a powerful phenomenon in modern medicine, and future psychedelic researchers ought to pay particular attention to its potential role in PAP. If researchers are aware of the positive influences that set and setting may have on the psychedelic experience, then these variables may be suitably bolstered in order to influence clinical outcomes. Despite the difficulties of creating a robust double-blind placebo controlled study using psilocybin, future work should aim to elucidate the degree to which the placebo response is responsible for potential clinical outcomes. This could be investigated by manipulating the expectancy of participants (outside of a clinical setting, for ethical reasons) or by, for example, correlating the prior suggestibility of a patient with the outcome of a PAP clinical trial.

5 - Insights from Meditation Research

Meditation and mindfulness-based practices deserve some attention in this literature review for two reasons. Firstly, there's evidence that meditation and mindfulness-based practices and psychedelics have some phenomenological and neurobiological similarities (Carhart-Harris, 2018; Carhart-Harris et al., 2014; Millière et al., 2018). Secondly, due to imposed restrictions on psychedelic research, there is a larger ongoing research effort investigating the effects of meditative states and mindfulness-based practices. Therefore, due to the similarities between meditative states and psychedelic experiences, meditation research may serve to shed some light on whether these practices and PAP share a similar mechanism that underpins their clinical efficacy.

5.1 A Brief Introduction to Mindfulness and Meditation

Meditative and mindfulness-based practices have generated a large amount of interest from the scientific community in the past several decades, as well as the term 'mindfulness' entering the secular public domain (Kabat-Zinn, 1982). The terms 'meditation' and 'mindfulness' have been used in a rather liberal fashion, and deserve some clarification. Meditation is derived from the Latin word "meditari", meaning engaging in contemplation or reflection (Chiesa & Malinowski, 2011). There are a variety of meditation

practices that are mentioned in the contemplative literature, each with their own idiosyncrasies and objectives. For the sake of brevity the list of meditative practices mentioned in this review will not be exhaustive (for an extensive review on the taxonomy of meditative practices see (Nash et al., 2013). While the meditative research has attempted to focus primarily on one type of meditation, it is worth noting that experienced meditators will develop a holistic practice, and rarely focus solely on one specific meditative technique[2]. Mindfulness suffers more semantic ambiguity, as there is still not a universal single definition of the phenomenon (for the promises and pitfalls of mindfulness research, see Van Dam et al., 2018). However, for the purpose of this review, mindfulness will be defined as moment-to-moment non-judgemental and non-reactive awareness, cultivated through purposeful contemplative practice (Grossman et al., 2004; Kabat-Zinn, 2011).

Cognitive neuroscience has more recently attempted to distinguish the differences between specific practices, as they are characterised by different techniques and result in different biomarkers and outcomes. To exemplify the distinction between specific meditative practices, the differences between focused attention meditation (FA) and open monitoring meditation (OM) will briefly be explored. Further to this, more clinically minded and secular practices such as mindfulness-based stress reduction (MBSR; Kabat-Zinn, 1990) and mindfulness-based cognitive therapy (MBCT; Segal et al., 2002) will also be presented.

In FA meditation, the main objective of the practice is to rest the attention on an explicit object of focus (e.g., the breath), and constantly monitor the quality of attention (Lutz et al., 2008). When the mind wanders, it is the practitioners aim to develop the meta-cognitive abilities to recognise that the focus no longer remains on the object of meditation, which then leads the practitioner to non-judgmentally return to the explicit object of focus. In OM meditation, however, there is no explicit object of focus. Rather, there is no distinction between selection or deselection of attention (Lutz et al., 2008). The practitioner simply attends to any qualia that may emerge, and develop their ability to remain in a non-judgmental monitoring state.

MBSR, however, is a secular approach that combines group work with daily homework assignments to encourage patients to cultivate the ability to observe thoughts as they come and go with dispassionate and non evaluative judgement (Grossman et al., 2004) in order to minimise the impact of stress. Further to this, the 8-10 week programme revolves around the teaching of meditative and yogic practices, as well as educating participants about the pathophysiology of stress (Bishop, 2002). MBCT is a more clinically-minded approach, which combines the meditative components of the MBSR programme with aspects of cognitive behavioural therapy (Beck, 1979).

5.2 Clinical Effects of Mindfulness Based Practices

There have been promising results when using mindfulness based practices such as MBSR and MBCT as clinical interventions. Meta-analyses that have investigated the effects of MBCT on major depression have found that the therapy is efficacious for relapse prevention in patients with recurrent depression (Chiesa & Serretti, 2011; Kuyken et al., 2008; Piet & Hougaard, 2011). Other meta-analyses have found that MBSR may significantly reduce stress levels in non-clinical populations (Chiesa & Serretti, 2009; Grossman et al., 2004). However, the studies that purport to investigate the effects of these mindfulness-based interventions suffer from a lack of standardisation, heterogeneous research protocols, and small sample sizes. Therefore, these methodological shortcomings, coupled with the fundamental aspect of group therapy being a major confounding factor that may contribute to positive clinical outcomes, make it difficult to reliably conclude that the meditative aspects are solely responsible for clinical improvement.

5.3 Neurobiological Similarities Between Meditative and Psychedelic States

Outside of clinical research, cognitive neuroscience has found striking similarities in the neurobiology of deep meditative states and the psychedelic state. It has been reported that, during deep meditative states, there is decreased activity in key nodes of the DMN, such as the PCC (Brewer et al., 2013; Lutz et al., 2016; Pagnoni, 2012) and the mPFC (Brewer et al., 2011; Farb et al., 2013; Scheibner et al., 2017). This corresponds to the objectives of various meditative practices; DMN activity has been consistently associated with mind wandering (Mason et al., 2007) and self-reflective thought (Sheline et al., 2009; Gusnard et al., 2001), and shows demonstrable anticorrelation with task positive networks (Fox et al., 2005; Kelly et al., 2008). Therefore, the reduction in DMN activity, most often in experienced practitioners, demonstrates that these practitioners are able to follow the objective of the meditation, rather than becoming distracted by spontaneous thoughts arising. Similarly, it has been demonstrated that activity in key nodes of the DMN decrease after the administration of psilocybin (Carhart-Harris et al., 2012), and other psychedelics (Carhart-Harris et al., 2016b; Palhano-Fontes et al., 2015).

5.4 Mystical Experiences and Meditation

As discussed earlier in section 3.5, the subjective effects of high doses of psilocybin are often characterised by a sense of unity, disintegration of the sense of self, and loss of concept of space and time (Stace, 1960; Hood, 1975). The phenomenology that results, or can happen, during deep meditative states have also been characterised similarly. Neurophenomenological studies of

2 This is corroborated by the fact that the Pali and Sanskrit term, bhāvanā, which is often translated as meditation, has a different connotation than "meditari". It more literally translates as "cultivating" (Chiesa & Malinowski, 2011). Therefore, different types of meditation practice may, by definition, allow the cultivation of different traits; Loving-Kindness meditation can help cultivate compassion for yourself and others, while Focused Attention meditation allows one to develop executive control functions.

Table 1: A table summarising the outcomes of psychopharmacological trials using PAP.
*Effect sizes vary due to the two different counterbalanced group (high dose 1st vs. low dose 1st). **Hedges' g was used as it is more appropriate for small sample sizes.

Publication & Study Design	Patient Population	Primary Outcome Measures and Experimental Session Dosages	Effect Sizes of Primary Outcomes
Grob et al. (2011) Double-blind placebo-controlled (niacin) crossover. Pilot study for existential distress in cancer patients	N=12 advanced stage cancer patients Diagnoses of acute stress disorder, generalized anxiety disorder (GAD), anxiety disorder due to cancer or adjustment disorder due to cancer.	Beck Depression Inventory (BDI); State Trait Anxiety Index Trait (STAI-T); State Trait Anxiety Index State (STAI-S) Two treatment sessions several weeks apart. Counterbalanced order of: - Session 1: 14 mg/70kg oral psilocybin - Session 2: 250mg niacin	BDI (p=.03) at 6-month follow up STAI-T (p=0.001; p=0.03) at 1-month and 3-month respectively
Griffiths et al. (2016) Double-blind placebo-controlled (low psilo dose) crossover for cancer-related anxiety and depression	N=51 advanced stage cancer patients Diagnosed with chronic adjustment disorder (CAD) with anxiety (11), CAD with mixed anxiety and depressed mood (11), dysthymic disorder (5), GAD (5), MDD (14), dual diagnosis of GAD and MDD (4), GAD and dysthymic disorder (1)	GRID-Hamilton Depression Rating Scale (GRID-HAMD-17); BDI; Hamilton Anxiety Rating Scale (HAM-A); Hospital Anxiety and Depression Scale (HADS); STAI Two treatment sessions ~5 weeks apart. Counterbalanced order of: - Session 1: low dose of psilocybin (22 mg/70kg or 30 mg/70kg) - Session 2: high dose of psilocybin (1 mg/70kg or 3 mg/70kg)	Post-high dose (5-weeks after session): GRID-HAMD-17 (p<0.001; d=0.86-1.04*) BDI (p<0.01-0.001; d=1.24-1.39) HAM-A (p<0.001; d=1.14-1.16) 6-month follow up: GRID-HAMD-17 (d=1.24-1.3) BDI (d=1.26-1.5) HAM-A (d=1.17-1.19)
Ross et al. (2016) Double-blind, placebo-controlled (niacin), crossover study for clinically significant anxiety and depression in cancer patients	N=29 patients, 62% of which with advanced cancers Diagnosed with adjustment disorder (26) or GAD (3)	BDI; HADS; HAD-A; HADS depression (HADS-D); Total HADS combined score (HADS-T); STAI-S; STAI-T Two treatment sessions ~7 weeks apart. Counterbalanced order of: - Session 1: 21mg/70kg of psilocybin - Session 2: 250mg niacin	Pre-crossover 7-weeks post-dose 1: HADS-T (p<0.001; d=1.36) BDI (p<0.05; d=0.82) HADS-D (p<0.01; d=0.98) Final remission rates 26 weeks post session 2: BDI remission rates ~60% for niacin 1st group; ~80% for psilocybin 1st group
Carhart-Harris et al. (2016) Open-label pilot study for treatment-resistant major depression (TRD)	N=12 patients with TRD Average illness length = 18yrs Patients unresponsive to both medication & various forms of psychotherapy	Quick Inventory of Depressive Symptoms (QIDS); BDI; HAM-D Two treatment sessions 1 week apart: - Session 1: low dose of psilocybin (10mg/70kg) - Session 2: high dose of psilocybin (25mg/70kg)	QIDS post session 2: 1-week (p=0.002; g**=3.1) 2-weeks (p=0.002; g=3.2) 3-months (p=0.003; g=2.0) BDI post session 2: 1-week (p=0.002; g= 3.2) 3-months (p=0.002; g=2.0) HAM-D post session 2: 1-week (p=0.003; g=2.4) BDI remission rates: 58% of patients at 3-months post session 2
Carhart-Harris et al. (2018) Extension of Carhart-Harris et al. (2016) 8 extra patients included Open-label feasibility study.	N=20 patients with severe or very severe (18) or moderate (2) unipolar TRD Average illness length ~18 years Median failed previous medications = 4	QIDS-SR16; BDI; STAI; HAM-D Two treatment sessions 1 week apart: - Session 1: low dose of psilocybin (10mg/70kg) - Session 2: high dose of psilocybin (25mg/70kg)	QIDS-SR16 post session 2: 1-week (p<0.001; d=2.2) 2-weeks (p<0.001; d=2.2) 6-months (p=0.0035; d=1.6) BDI p session 2: 1-week (p<0.001; d=2.5) 3-months (p<0.001; d=1.4) 6-months (p<0.001; d=1.4)

meditators (Thompson et al., 2005) have enabled neuroscientists to inquire into the phenomenology of deep meditative states while simultaneously investigating the concurrent neural mechanisms that may underpin these states. Notably, Dor-Ziderman et al. (2016) investigated the neural mechanisms that underpinned the graded phenomenon of meditatively-induced disruption of an experienced meditation practitioner's sense-of-boundaries (SB) - the division of experience between a perceived "self" against a "world". This blurring of boundaries between the "self" and the "world" is strikingly similar to the original definition of a mystical experience (Stace, 1960), and maps onto the phenomenology that characterises aspects of the psychedelic state. Dor-Ziderman et al. (2016) found that as the participant went from a normal SB to a state where SB disappeared, there were significant negative regression coefficient values in beta band frequencies (22-33Hz). This effect was localised to regions comprising the temporoparietal junction (TPJ), and the middle/posterior cingulate gyrus (M/PCC), regions comprising of the DMN. Not only does this blurring of the practitioner's SB map directly onto the original definition of a mystical experience (disintegration of sense of self), but this beta-band cortical desynchronisation has previously been exhibited in the psychedelic state (Muthukumaraswamy et al., 2013). This beta band power decrease in regions comprising of the DMN has also been found in meditator's that were instructed to attenuate "minimal" self-awareness (Dor-Ziderman et al., 2013), characterised by a sense of agency and ownership with a focus on present momentary experience.

Berkovich-Ohana et al. (2013) also used a neurophenomenological approach with MEG to investigate the effects of an alteration in the experience of time and space. Again, this phenomenology as a consequence of meditation maps directly onto the temporal and spatial factors included in the definition of a mystical experience (Stace, 1960; Hood, 1975). In the study, 11 mindfulness meditators were instructed to volitionally produce states that are associated with timelessness and spacelessness. The researchers found significant alterations in theta band activity. Further to this, the disruption in theta band activity was localised to the TPJ and bilateral cingulate cortex/precuneus (PCC/Prc) for both spacelessness and timelessness. As illustrated above, disruption in the activity of these regions are both central to the blurring of SB, attenuation of "minimal" self-awareness and the psychedelic state.

5.5 Predictive Processing & Meditation

In a predictive processing framework, meditative practitioners may down-regulate overly precise (rigid) priors through the continued training of attention and awareness, and the intentional prevention of mind-wandering and self-related thoughts. This is corroborated by evidence of the down regulation of activity in key nodes of the DMN during deep meditative states, as presented in the previous sections. Psilocybin, however, may down-regulate key nodes of the DMN, and associated high-level priors, through $5HT_{2A}R$ agonism. We speculate that this analogous effect on rigid priors may underlie some of the phenomenological, neurobiological and clinical outcomes associated with both meditation and PAP.

To exemplify this mechanism, a meditative practice can be explained through a predictive processing framework (Lutz et al., 2019; Pagnoni, 2019). In the predictive processing framework, the overarching aim of the organism is to minimise the average uncertainty over a period of time - as approximated by the prediction error. Again, the prediction error is the mismatch between incoming sensory signals and the top-down predictions already held. However, the prediction error signals that are travelling up the cortical hierarchy may be downweighted - if the signal is deemed unreliable - which then lends to the favouring of prior learnt information. In this case, the brain uses prevision-weighting to estimate the expected uncertainty of incoming sensory signals. In a meditative practice, such as Focused Attention, the meditator's objective is to develop the ability to attend more readily to incoming sensory information, and pay less attention to distracting thought patterns. When the mind wanders, the meditators are encouraged to non-judgmentally return to the object at hand (e.g. the breath). Within the predictive processing framework, the increased allocation of attentional resources to these bottom up sensory signals corresponds to localised neuromodulatory activity (Feldman & Friston, 2010). By allocating these attentional resources towards bottom-up sensory signals, and thus not engaging in mind-wandering activity - facilitated by high-level cortical areas such as the DMN - the process of meditation allows one to assign less precision to priors. If these priors are over-precise (and maladaptive), meditation can then be utilised as an efficacious treatment in depressive disorders (in a predictive processing framework).

It should briefly be mentioned that the hallmark neurobiological effects and phenomenology of deep meditative states may not be achieved through a short term practice. However, participants are able to experience these states with psilocybin in one session, due to the pharmacologically-induced mechanism of $5HT_{2A}R$ agonism. Therefore, PAP may be more suitable as a clinical intervention to bring more immediate therapeutic relief to patients that require it (such as existentially distressed cancer patients, or patients suffering from TRD). However, we may speculate that the benefits of PAP may be more transient than a long term meditation practice.

6 - The Network Theory - Future Directions for Psychedelic Research

In the previous sections, focus has been distributed between the neurobiological effects of psilocybin, the potential psycho-spiritual mediatory mechanisms and extra-pharmacological factors that determine clinical outcome using PAP. By acknowledging these factors, future psychedelic research could contribute to a more interdisciplinary narrative within the psychiatric paradigm, rather than the dominating research initiative that emerged a decade ago (Insel et al., 2010). This initiative served to primarily promote neuroscientific and genomic explorations into underpinning psychopathologies. This led many researchers to adopt a reductionist approach to mental health research, searching primarily for biomarkers and neurological substrates to explain the

manifestation of mental health disorders. This perspective has arguably been damaging for the fields of psychiatry and clinical psychology, as it ignores the interacting elements that contribute to an individual's psychological and neurobiological functioning. For example, a recent meta-analysis has conceded that identifying a single biomarker in depression is unrealistic, due to the heterogeneous profile of the disorder (Gururajan et al., 2016).

Unlike physiological issues, mental health issues are complex and multi-faceted; it is not advantageous to adopt a reductionist approach to elucidate a unifying mechanism that serves to explain a mental health issue (Borsboom, 2017). PAP in a clinical setting has demonstrated robust efficacy for a myriad of mental health issues (Thomas et al., 2017). Moreover, it is acknowledged, and argued through this review, that the route to clinical improvement using PAP is more complex than simply a pharmacologically-induced mechanism. Although it is difficult to disentangle the psycho-spiritual and neurobiological mechanisms that underpin the efficacy of PAP as a clinical intervention, the contribution of both of these factors should be recognised and incorporated into psychedelic clinical neuroscience.

A parallel theory that also seeks to reassess reductionism in psychopathology research is arising - the network theory of mental disorders (Borsboom, 2017). According to the network theory, psychopathological issues emerge due to the interaction of symptoms in a complex dynamic network. These symptoms (or nodes) are causally connected to each other through psychological, biological and societal mechanisms (Borsboom, 2017). When these connections between symptoms are particularly strong, the causal interplay between these symptoms will set up a self-sustaining feedback loop, which then facilitates the emergence of a corresponding mental disorder (Borsboom & Cramer, 2013). The network theory has given rise to statistical techniques that seek to map the dynamic structure of symptom networks in a variety of psychopathologies including major depression (Boschloo et al., 2016; Cramer et al., 2016; Fried et al., 2016; van Borkulo et al., 2015), substance abuse (Rhemtulla et al., 2016) and anxiety disorders (Beard et al., 2016; Heeren & McNally, 2016). The network theory is gaining increasing empirical support (Fried et al., 2017), as the approach has identified network characteristics that may preclude the emergence of depressive episodes (van de Leemput et al., 2014; Wichers et al., 2016), has been able to demonstrate how major depression can manifest and maintain itself (Cramer et al., 2016), and parsimoniously explains the existence of high rates of comorbidity in specific mental health disorders (Cramer et al., 2010). Further to this, the theory provides a differing narrative to the latent model of psychopathology - that symptoms occur due to the presence of a latent psychopathological variable (i.e. the disease). For a comprehensive introduction to the network theory, see Borsboom (2017).

The network theory recognises the multiple realisability of psychopathologies. Borsboom et al. (2019) argue that mental disorders can't solely be explained biologically, or in a manner that pertains to explanatory reductionism. That is, the research initiative that aims to explain the occurrence of mental disorders (a higher-level theoretical term) through the identification of one mechanism (such as a biological construct) has, by and large, failed. The network model of mental disorders, however, resists this strategy. It recognises the heterogeneity between individuals, and maps network structures and connectivity based on the individual. The theory also does not use sweeping statements to describe one central mechanism to the emergence of such mental disorders. Moreover, the causal relations between symptoms in a network structure are described as involving intentional information. That is, they involve beliefs, desires and emotions, that describe the mental states that underpin certain symptoms. Borsboom et al. (2019) give an example of the causal connections between thoughts of low self-worth and self-reproach and thoughts of suicide, and highlight that there are correlations between these variables (Cramer et al., 2010; Dori & Overholser, 1999; Wild et al., 2004). Through the use of intentional information, it may be explained why there exists a correlation between these variables: being convinced of a lack of self-worth will lead to the entertainment of ideas that one may be a burden to society. As a result, the idea that one is a burden to society can spark thoughts that suicide may be the best option, as they may conclude that society would be better off without them. Consequently, suicidal ideation may occur.

The self-sustaining feedback loops that lead to the emergence of mental disorders, and the intentional information that underpin these causal connections, is strikingly similar to the predictive processing approach of categorising depressive disorders. As discussed in section 2.3, depression may be driven by abnormally precise and maladaptive priors (Edwards et al., 2012; Clark et al., 2018; Kube et al., 2019). These overprecise priors then have a top down inhibiting effect on bottom up sensory information, so that if discounting information is encountered, the top down effect will be to downweight the prediction error travelling up the hierarchy. To exemplify, if someone with major depression has a prior belief, such as "none of my friends enjoy my company", this overprecise prior will perpetuate the maladaptive belief that they are not liked by their friends, regardless of how much they engage in ostensibly positive social activities. Put simply, the belief will outweigh any evidence from the world that their friends do enjoy their company. This can also foster a self-fulfilling prophecy: the over precise prior may causally influence other symptoms in a network; the belief that one is a burden then leads to that individual not seeking any more social contact, which, in turn, may further exacerbate symptoms. Thus, the predictive processing view of depression also serves to explain how depressive symptoms are maintained in an individual through the inherent tendency to confirm overly-precise and problematic priors.

The network theory is being mentioned here as it directly relates to the mechanism that is proposed in this thesis explaining why PAP may be so useful in treating depressive disorders. The downweighting of over-precise maladaptive priors, through 5-HT_{2A}R agonism and the potential mediation of mystical and spiritual experiences, may directly relate to the reorganisation of the network structure in individuals that respond to PAP. We may hypothesise that, due to the downweighting of over-precise

maladaptive priors, PAP may reorganise the network structure of individuals that are responsive to the treatment. By using the network approach, future researchers have several opportunities. Firstly, a network approach provides a deeper insight into participants day to day fluctuations in mood and depressive scores. This is due to the network approach requiring time-series data, which is used to calculate partial correlations between symptoms. Secondly, it is possible to compare and contrast the way that PAP has influenced the network structure. For example, PAP may be efficacious in treating certain mental health disorders, as the intervention may act on nodes with a high degree of centrality (Fried et al., 2016), which would serve to mitigate an individual's potential to relapse into a depressive episode. Alternatively, the intervention could target the connections between bridge symptoms, that function as bridges between differing mental health disorders (Borsboom et al., 2011). Thirdly and finally, PAP, and psychedelic research in general, has provided a unique insight into complex psychological changes (Lyons & Carhart-Harris, 2018; MacLean et al., 2011) and mystical experiences (Griffiths et al., 2006; 2011) that would otherwise be impossible to study in a lab controlled setting. The profound psychological and clinical effects of psychedelic use equips researchers with unique opportunities to investigate how a single intervention can affect the network structure.

7 - Conclusion

One of the main explanatory gaps within psychedelic clinical neuroscience is the fact that researchers are still yet to understand which subjective and neurobiological effects of psilocybin facilitate clinical improvement (Swanson, 2018). As such, this review has sought to use a predictive processing framework to summarise the key mechanisms that may contribute to clinical improvement when PAP is used as a treatment for depressive disorders. This primarily includes the pharmacologically-induced mechanism of $5HT_{2A}R$ agonism, which serves to reduce the precision of high-level maladaptive priors during the psychedelic experience. These over-precise maladaptive priors are also a commonly cited mechanism in predictive processing theories of depressive disorders (Edwards et al., 2012; Clark et al., 2018; Kube et al., 2019). $5HT_{2A}R$ agonism provides a window of opportunity for effective psychotherapy.

What must be emphasised, however, is that this review does not endorse a solely biological mechanism in which PAP proves to be effective. It has been demonstrated throughout this review that $5HT_{2A}R$ agonism may be of great importance, yet there are many other contributing factors. These arguably include extra pharmacological factors such as the placebo response, the setting of psilocybin administration, patient mood and expectation, and the presence of mystical/peak experiences during the psychedelic session. If these factors interact, and the patient has a positive appraisal of the experience that they can integrate into their lives, this may serve to occasion complex psychological changes leading to positive clinical outcomes. We speculate that these complex psychological changes may be best tested by mapping the network structure of patients (Borsboom, 2017).

7.1 Hope for the Future

We approach the future of psychedelic clinical and cognitive neuroscience with cautious optimism. There are still many critiques of psychedelic research. Namely, the current clinical studies are either open-label or find it difficult to use an effective placebo, have small sample sizes, and have an extensive screening process. However, gaining access to psilocybin for scientific research is time-consuming and cumbersome. Therefore, the fault of small sample sizes may not solely lie in the hands of researchers. Further to this, although this screening process necessarily errs on the side of caution - there is associated harm with high doses of psychedelics, especially for those at risk of psychosis - it also generates problems for the generalisation to a wider sample of people. How effective is PAP in a wider demographic with less psychological screening? The answer is still unknown. Only continuous future psychedelic research will be able to shed light on this, and other pressing questions in the realms of consciousness and neuroscience.

Painting Hypotheses, Cooking Methods, and Composing Results:

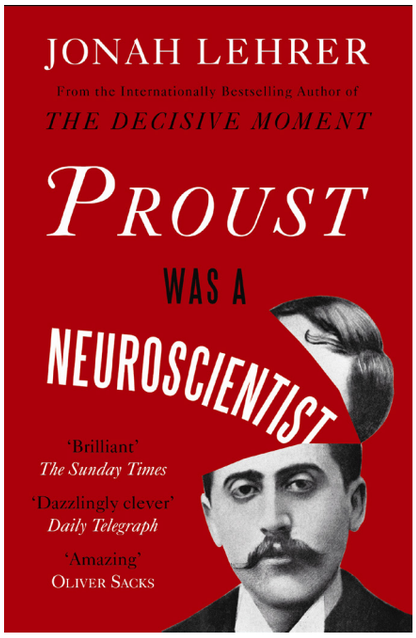
A Review on "Proust was a Neuroscientist"

Rebecca Dyer
Ada Örken

Jonah Lehrer, the author of *Proust was a Neuroscientist*, studied neuroscience at University of Columbia. Alongside his studies, he worked as a neuroscience lab technician. Here, he started reading Proust. Although he thought what Proust wrote differed significantly from the lab's work, he realised there were some overlaps. "The novelist had predicted my experiments," Lehrer wrote in the introduction of his book. This revelation eventually led him to the realisation that past novelists and creatives alike had, in fact, predicted, postulated upon and even utilised neuroscientific discoveries that had yet to be made. The author takes the reader on a poetic journey across the bridge between the creative and scientific disciplines. While the poets and authors theorised about the nature of the mind's relationship with the body and our capacity for free will, chefs, painters and musicians demonstrated faculties of our perception and cognition which we had yet to discover by overcoming the conventions of their fields. In essence, *Proust was a Neuroscientist* breaks the boundaries between the creative and scientific disciplines, and demonstrates to the reader that the creatives are just as much interrogators of the unknown, and utilisers of their observations as neuroscientists are.

The first chapter begins with a description of Walt Whitman's work and experiences, expertly interweaving the two to express how Whitman's observations informed his writing in the same way that a scientist's observations inform their hypotheses and later conclusions. For example, Whitman's observations of those who experienced phantom limb syndrome after amputations during the Second World War was evidence for him that the mind and the body cannot be separated. Lehrer elegantly expresses Whitman's belief in the following sentence: "To whip a man's body is to whip a man's soul". Lehrer then moves on to discuss neuroscientific observations of this concept, describing patients whose loss of proprioception resulted in a numbing of the emotional experience. As such, the artistic poetry of Whitman described a concept that would only later be investigated in neuroscientific practice.

Arising from Lehrer's clever entanglement of the experiences of the creatives and their resultant theories, *Proust was a Neuroscientist* is actually an art and science history book. It follows the work of eight artists and the relationship of these



Published by Canongate Books, 2011

works to neuroscience. However, it does more than just demonstrate the links. Lehrer tells us stories of scientific discoveries, art movements, artists and scientists. For example, he introduces the reader to the invention of photography, Gestalt psychologists, impressionism, Oliver Sacks and The Man who Mistook his Wife for a Hat, Emile Zola, and Hubel and Weisel's works on vision, all in one chapter on Cezanne. In that sense, Lehrer boldly pursues an interdisciplinary point of view and tackles scientific concepts from fields which are less familiar to him, and this is a wonderful attribute of the book. However, the frequent jumping from one subject to another occasionally makes the book difficult to follow. If you have a neuroscientific background, it is really nice to read about some history in a story-like fashion. Formal education usually teaches results, leaving the stories behind the discoveries forgotten and undermined. For example, most of us would know about Sperry and Gazzaniga's work on split brain patients and their discovery of the asymmetry of hemispheres. However, very few of us know any stories about their discovery process. You may read their

and many others' stories in this book. Through its storytelling, the book has the potential to remind us of some of the basics of neuroscience and, therefore, could be a great source of inspiration.

The interdisciplinarity of the book is further demonstrated by Lehrer's highly understandable writing style. Lehrer provides the reader with the background knowledge required to understand everything that he presents within his book in a story-like manner, at a depth that only the combination of the two disciplines could achieve. Therefore, the book can be approached and easily read by those from artistic or scientific backgrounds, or possibly from entirely different fields. This universal writing style is inherently necessary for this new age of theorisation and discovery; it is the bedrock upon which different disciplines can communicate. However, it must be said that the beginnings of Lehrer's descriptions of scientific discoveries within each paragraph are somewhat blurred. Consequently, it can be difficult to determine where the creative ends and the scientific begins. This may be by design, and further encapsulates Lehrer's point that the creative is not so different from the scientific. However, it can make for difficult reading, as the reader's perception must switch from the poetic to the rigorous thought process. A final point about his writing style is that it feels somewhat poetic in itself, clearly demonstrating the impact of his love of the creative as he makes his way through his own scientific discipline.

Science has its way of doing things. Scientists follow a certain method in their studies. These methods may even differ from one discipline to another. Today, science is so specialised that it is hard to find a common language between two sciences, such as physics and biology, let alone a common language between art and science. Lehrer suggests that this common language is important for scientific development. His writing style is not only accessible, but also a reflection of the point he is trying to make: the brain can be understood from a multitude of disciplines. The reductionist methodology of science makes one blind to what extends beyond what is conventionally believed to be scientific. However, the inspiration you are looking for can be hidden in a novel, in a symphony or in one of your favourite paintings. Therefore, science should not undermine art and be aware of what artists can sense and present.

Lehrer does not only suggest that scientific methodology needs to change and communicate better with arts. He proposes better communication in both directions since it is highly possible that art also has a lot to learn from science. Gertrude Stein, for example, was a scientist before she became an avant-garde writer. Lehrer narrates how her scientific work in a psychology lab with William James shaped her future work and her understanding of language. Yet, the interaction between art and science does not always need to be through a formal education like Gertrude Stein's. An artist without any scientific background should also be able to use science in their works; Lehrer calls this collaboration of science and art 'the fourth culture', moving beyond cultures of art, science and popular science. He suggests that preceding cultures need to give up some old habits in order to reach there.

Despite Lehrer's obscure history of plagiarism which led to his firing from The New York Times, the publisher's investigation did not find any problems with *Proust was a Neuroscientist* and the book remained in print. Therefore, we can safely recommend the book. Overall, it is an inherently interdisciplinary book, accessible for those from a variety of disciplines. This accessibility allows for communication between the scientific and artistic domains in a way that is so rarely successfully achieved. The writing style and information consistently reflect this interdisciplinarity as Lehrer clearly makes his point: neuroscience is not just for the scientists; the creatives can just as successfully formulate hypotheses and make observations, void of the so-called scientific method. His book is a clear demonstration of the idea that the sciences should not be isolated from the creative; instead the two should work together. After all, science is merely the act of asking questions about our world and attempting to answer them. This act is not isolated to scientists despite typically being treated as such. Therefore, science should be informed by the creative thinking of those we so often exclude.

Time Distortions: A Review

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Background: Time distortions are substantial alterations in the subjective experience of time. Since they are classified as perceptual distortions, they are considered part of the Alice in Wonderland syndrome (AIWS). Little is known about AIWS, and even less about time distortions. **Objective:** I here review original case descriptions and research papers on time distortions, irrespective of their clinical context. I place these findings in the context of what is known about normal time perception and about subjective, psychological time experience. **Findings:** In the 11 papers found eligible for inclusion, slow-motion and quick-motion phenomena were described almost exclusively, either occurring separately or in combination. The majority of these cases were accompanied by other perceptual distortions and caused by neurologic or psychiatric disorders. **Conclusion:** In theory, time distortions may take many forms, but in the literature reviewed here, mainly descriptions of slow-motion and quick-motion phenomena were found. Judging by the clinical context in which they were described, like other AIWS symptoms, these phenomena are not specific to any underlying cause. An exception would seem to be the fragmentation of time structure reported by patients diagnosed with schizophrenia during the post-psychotic phase. Based on my findings, I make a case for the revaluation of time distortions in classifications of psychopathology and formulate directions for further research.

Introduction

Subjective experience of time

The sense of time passing is dependent on one's personal experience. Sometimes time may seem to fly, while at other times it may seem to last forever. Thus, time experience has a subjective, phenomenological aspect to it that does not always correspond with objective time, as measured by clocks and other chronometers. While we all have experienced the feeling of time speeding up or slowing down, alterations in the experience of time can also be more profound. Such profound time distortions have been described in the context of psychiatric and neurological conditions, as well as in intoxications (Teixeira et al., 2013; Thönes & Oberfeld, 2015; Tysk, 1984a). Patients undergoing such time distortions commonly complain of an unusual speeding up or slowing down of their personal time compared to the actual clock time. Unlike physiological alterations in the experience of time, this is not always situation-dependent and may cause distress and a decline of quality of life (Vogel et al., 2019; Vogel, Krämer, Schoofs, Kupke, & Vogeley, 2018). Time distortion, regardless of the underlying pathology (psychiatric, neurologic, or substance-related), is classified as a perceptual distortion and hence considered characteristic of Alice in Wonderland Syndrome (Blom, 2016).

Alice in Wonderland Syndrome

Alice in Wonderland Syndrome (AIWS) is a rare, usually paroxysmal disorder characterized by a broad range of perceptual distortions. The name takes inspiration from the famous English book character, a young woman called Alice (Carroll, 1865). Alice experiences many peculiar changes to her body size and her surroundings, and alterations of space and time throughout her adventure. AIWS is likewise characterized by perceptual distortions. This 'third group of perceptual disorders' (hallucinations and illusions constituting the first two groups) has been much neglected and is therefore hardly known among health professionals (Blom, 2016), even though its underlying causes include neurologic and psychiatric diseases that merit proper clinical attention, such as migraine, CNS infection, schizophrenia and major depressive disorder (Mizuno, Kashima, Chiba, Murakami, & Asai, 1998; O'Toole & Modestino, 2017; Weissenstein, Luchter, & Bittmann, 2014; Yokoyama, Okamura, Takahashi, Momose, & Kondo, 2017). The operational criteria of AIWS include a long list of visual and other perceptual distortions that may occur individually or (less frequently) in combination with each other. The most commonly reported ones are perceiving objects to be smaller or larger (micro- or macropsia) or to be located farther away (teleopsia) (Liu, Liu, Liu, & Liu, 2014). Furthermore, patients themselves may feel to be larger or smaller than in reality (micro- or macrosomatognosia) (for review, see Blom, 2016), and experience depersonalization, derealization or time distortions (Mizuno et al., 1998; Perdices, 2018). Time distortions take various forms in this syndrome. Thus, time can be felt as accelerated or decelerated to the point of complete stagnation, referred to as quick- and slow-motion phenomena. Although less frequently, patients may also experience time as behaving in fairly bizarre ways, i.e., moving in circles, going backwards, being fragmented, or repeating itself over and over again (Jaspers, 1997, pp. 82-87). Because little is known about these phenomena, our goal is to review research papers and case reports about subjective time distortions, whether or not classified by the authors themselves as a manifestation of AIWS, and irrespective of the underlying cause.

Methods

A systematic literature search was carried out in PubMed, PsycINFO, and Google Scholar up until April 1, 2020, using the search terms Alice in Wonderland syndrome, time distortion, time perception, temporality, temporal alteration, timing deficit, time experience, and variants thereof. Theoretical and opinion papers were excluded (Ghaemi, 2007; Ratcliffe, 2012). In addition, papers were excluded when the temporal alterations reported did not comply with the definition of time distortions, e.g. deficits in duration estimation rather than experiences of the perceptual distortion of time (Elvevåg et al., 2003). From all eligible reports and research papers, the following data were extracted: i) year of publication, ii) sex and age of the patient, iii) phenomenological characteristics, iv) clinical diagnosis, v) test results, vi) type of treatment, and vii) outcome.

Results

The online search initially yielded 14 papers on time distortions in the context of AIWS, of which three were clinical reports, and one was an empirical study. Seven other papers described patients experiencing time alterations which, in some cases, could be interpreted as time distortions, although the authors do not mention the term AIWS. Together the latter seven articles described 135 patients, while all reports together described 139 patients (Table 1).

All four papers about patients with AIWS describe altered speed of time flow (quick- and/or slow-motion phenomena). The most recent clinical paper reported on both phenomena (Naarden, ter Meulen, van der Weele, & Blom, 2019). These time distortions were experienced in the context of Creutzfeldt-Jakob disease, an extremely rare neurodegenerative disorder (i.e. prion disease). The 68-year-old male patient described in that paper reported that the movements of people around him were either unrealistically decelerated or accelerated, which made him feel as if he were "...watching a Charlie Chaplin movie".

Another study reports on a 54-year-old man experiencing classic AIWS symptoms of metamorphopsia, distortion of body image, and an altered sense of time (Mizuno et al., 1998). In this case, the underlying cause was thought to be major depressive disorder. The patient experienced episodes of quick-motion phenomenon. Before hospitalization, he went for a haircut and by the time the hairdresser was finished with his hair he felt as if only a couple of seconds had passed. On another occasion, while waiting a long time for a doctor in a hospital, he felt that only several minutes had passed. Interestingly, despite the subjective feeling, during this episode the patient remained aware of objective time and could correctly judge the actual time span of several hours. The patient also reported that, while looking at traffic, he felt that cars were moving too quickly and felt great discomfort about it. CT, MRI, and EEG results were all normal. He was treated with benzodiazepines (lorazepam 1.5 mg/day). Upon this, the other AIWS symptoms resolved after two days of hospitalization, whereas the recurring episodes of time acceleration persisted for 3 months.

A similar case was reported by Yokoyama et al. (2017). To our knowledge, this is the only brain imaging study in this area. The authors describe a 63-year-old man who experienced two episodes of major depressive disorder (MDD) over a period of three years, complicated by body image distortions and an altered perception of distance and time (Yokoyama, Okamura, Takahashi, Momose,

Table 1: Summary of included case reports and research papers

Study	Type of study	Patients	Clinical diagnosis	Type of time distortion
Naarden, ter Meulen, van der Weele, and Blom (2019)	Case report	68-year-old male	Creutzfeldt-Jakob disease	quick- and slow-motion phenomena
Mizuno et al. (1998)	Case report	54-year-old male	Major depressive disorder	quick-motion phenomenon
Yokoyama et al. (2017)	Case report	63-year-old male	Major depressive disorder	quick-motion phenomenon
Jia and Miao (2018)	Empirical	male in late 20s	None	quick-motion phenomenon
Thönes and Oberfeld (2015)	Meta-analysis	433 patients (16 papers)	Depression	slow-motion phenomenon
Kitamura and Kumar (1982)	Empirical	13 males and 10 females, mean age 42.4	Major depressive disorder	slow-motion phenomenon
Blewett (1992)	Empirical	6 males mean age 34; 23 females mean age 39	Depression	slow-motion phenomenon
Vogel, Krämer, et al. (2018)	Empirical	15 males and 10 females mean age 47	Severe Depressive Episode	slow-motion phenomenon
Stanghellini et al. (2017)	Empirical	39 males and 61 females mean age 39.45	Major depressive disorder	slow-motion phenomenon
Freedman (1974)	Collection of autobiographical descriptions	7 patients	Schizophrenia	quick- and slow-motion phenomena
Vogel et al. (2019)	Empirical	15 males and 7 females	Schizophrenia	quick- and slow-motion phenomena and time fragmentation

& Kondo, 2017). As for time, the patient experienced days to be passing by in a split second. It appears that the patient described this experience as it was unfolding in the present moment rather than the recollection of it, and that it lasted the whole day. During the second episode the researchers obtained pre- and post-treatment PET scans which showed hypoperfusion of bilateral frontal regions, which they associated with depression, as well as bilateral hypermetabolism of the parietal and occipital lobes. Treatment with 12 sessions of electroconvulsive therapy, duloxetine (60 mg/day) and mirtazapine (45 mg/day) resulted in a complete resolution of the AIWS symptoms and the depression, and in a normalization of the metabolism of the parieto-occipital areas. Besides visual comparison of pre- and post-treatment PET images, the researchers also conducted statistical analyses of pre- and post-treatment brain scans. Bilateral posterior temporal cortex, occipital cortex, inferior parietal cortex, precuneus, and posterior cingulate cortex showed significantly decreased (i.e. normalized) metabolism after the analysis. As for frontal areas, although after treatment an increase in metabolism was visible, the effect was not statistically significant. The authors suggested that the findings could be related to positive symptoms (delusions) as well as to AIWS. Based on this assumption, they argued that there could be a common underlying metabolic abnormality shared by psychotic depression and AIWS. Although an altered sense of time and body perception has been described before in the context of depression (Thönes & Oberfeld, 2015), this is the only study that showed alterations of brain metabolism during the time distortions.

At present, only one study aimed to quantify and objectively measure time distortions in AIWS (Jia & Miao, 2018). The patient under study (a male in his late 20s) reported recurring episodes of time acceleration. The researchers tested his reaction time, based on the prediction that reactions to computerized tasks under these circumstances would be slower than normal. They found a significant slowing of the participant's reaction time during episodes of time distortion (five episodes in 13 months) compared to his own baseline. The authors regarded this finding as the first empirical demonstration of time distortions in AIWS.

In summary, the time distortions discussed so far, all co-occurred with other symptoms of AIWS such as micro- or macropsia, body schema illusions and alterations of the perception of space. The two types of time distortions described (i.e., slow-motion and quick-motion phenomena) either presented individually or in combination. In three of the four cases of AIWS an underlying cause was established (in two cases MDD, in one case prion disease).

Time distortions have also been described without referring to AIWS, notably in psychiatric conditions (Fuchs & Van Duppen, 2017; Kuhs, 1991; Thoenes & Oberfeld, 2017). Thus, the slow-motion phenomenon has been reported in patients suffering from either depression or schizophrenia (Ghaemi, 2007; Ratcliffe, 2012; Stanghellini et al., 2017). Patients with these diagnoses were requested to answer open-ended questions about personal time (Bech, 1975; Kitamura & Kumar, 1982), followed, in some studies, by qualitative content analysis (Vogel et al., 2019; Vogel, Krämer, et al., 2018). For the latter purpose, the authors created a tailor-made Time Questionnaire, the first part of which assesses the personal sense of time, and the second the subjective sense of the structure of time, i.e. the causal relation and directionality of past, present and future. The questionnaire was successfully validated in healthy participants (Vogel, Falter-Wagner, et al., 2018) and then applied to patients with MDD and schizophrenia in two separate studies (Vogel et al., 2019; Vogel, Krämer, et al., 2018). While answering the questions, the patients were encouraged to add their own narratives, thus providing the authors with sufficient material to conduct their systematic analysis.

In clinical practice, another method to assess alterations in time experience is the visual analogue scale (VAS) (Blewett, 1992; Bschor et al., 2004). The VAS represents a vertical line and its midpoint corresponds with a normal sense of time (globally comparable with objective time or clock time). Patients are asked to map their subjective time experience on the vertical bar, where a downward shift from the midpoint indicates a slowing down and an upward shift a speeding up of the sense of time.

A deceleration of the sense of time was reported most frequently by depressed patients. One meta-analysis on time distortions and estimation deficits of interval duration (16 papers in total; Thönes & Oberfeld, 2015) failed to show any significant effects of depression on duration judgment, but did demonstrate that subjective time experience was uniformly slowed down in depression. Kitamura & Kumar (1982) investigated time experience in depressed patients and matched controls using a self-rating questionnaire of time awareness. Their main finding, too, was a slowing of subjective time in the depressed group. Interestingly, this experience was not specific to any of the diagnostic subtypes of depression (endogenous, neurotic or depression with paranoid state). Similar results were obtained in depressed patients by Blewett (1992) using the VAS, which also showed that the severity of time distortions correlates positively with the severity of depression. Thus, patients with more severe depressive states also reported time passing much slower. Another finding of these studies was that time distortions are usually amenable to treatment of the depressive symptoms (Blewett, 1992; Kitamura & Kumar, 1982).

By means of the Time Questionnaire, Vogel et al. (2018) showed that reports of time distortions by depressed patients confirmed the previous reports. The patients almost uniformly reported a sense of deceleration, and sometimes even stagnation or freezing of time (Vogel, Krämer, et al., 2018). These results were in line with those of Stanghellini et al. (2017), who conducted a qualitative analysis of hundreds of subjective narratives about abnormal time experience in depressed patients. Their main finding involved decelerated time experience. In addition, the patients' experiences were dominated by the past rather than the present or the future, as if the past were invading the present experiences while the anticipation of the future was overshadowed and undermined by being predominantly focused on the past. Based on this, Vogel et al. (2018) even proposed that time distortion is not just another symptom of depression, but that MDD can be considered a "syndrome of disturbed lived time" (Vogel, Krämer, et al., 2018).

This conclusion is in agreement with the phenomenological psychopathology approach, according to which time distortion is regarded as the root of every other symptom in MDD (Stanghellini et al., 2017). This approach indicates that a subjective deceleration of time is indeed one of the prominent features of MDD and should therefore be addressed by practitioners while interviewing their patients.

Vivid descriptions of time distortions and "timelessness" are also found in autobiographical records of patients with psychotic symptoms (Freedman, 1974). Among other perceptual distortions and cognitive symptoms, some patients describe a sense of alteration or even complete loss of the sense of time passing. Most of them report a deceleration of subjective time or of perceiving the world in slow motion, although some distortions appear to be more complex, judging by the remark of one patient who wrote that "...a day might consist of weeks, of hours, of a minute, or frighteningly, of not even a second". It is not clear to us, whether the patients described their experiences during episodes of time distortion, or while looking back to that particular moment in the past, judged it to have lasted either shorter or longer.

The sense of an acceleration of time is rarely reported as an isolated phenomenon. That is, patients who report a speeding-up of time usually experience alternating states of deceleration and acceleration. Contrary to depression, reports about time experience alteration in schizophrenia are not homogeneous and the direction of change, i.e., speeding up or slowing down, has been related to this disease (Fuchs & Van Duppen, 2017; Stanghellini et al., 2016). Studies using the Time Questionnaire in schizophrenia revealed time distortions in the majority of patients (Vogel et al., 2019). They were most pronounced during acute phases of psychosis, and generally absent during post-psychotic phases. During post-psychotic phases, however, a fragmentation of time structure was sometimes found in these patients (Vogel et al., 2019). Specifically, this involved the loss of a subjective sense of continuity between the past, the present and the future. The patients experienced time as if it were cut into pieces, as opposed to a healthy sense of time flow from the past, via the present, into the future.

Another finding was that pathological time distortions tend to be situation-independent; the symptoms can be paroxysmal, without any clear triggers, or be persistent, likewise without any apparent connection with outside events (Vogel et al., 2019). This is different from alterations in the sense of time reported by healthy individuals (Zakay, 2014). It has therefore been speculated that the subjective deceleration of time in MDD can be regarded as an extreme case or an amplification of a slowing down of psychological time during unpleasant or uneventful situations (Stanghellini et al., 2017; Vogel, Krämer, et al., 2018).

Discussion

I reviewed eleven papers describing 139 patients who experienced time distortions. The main forms reported were slow-motion and quick-motion phenomena, and the majority of patients had an underlying diagnosis of MDD or schizophrenia, with the exception of one idiopathic case of AIWS and one case with prion disease. Some studies also described time fragmentation, although exclusively in the context of schizophrenia. I will interpret these findings in the context of what is known about the physiology of time perception and about subjective time experience, and explore the place of time distortions in classifications of psychopathology.

Physiology of time perception

The prevailing model conceptualizing the experience of time is the Scalar Expectancy Theory (SET) (Gibbon, Church, & Meck, 1984; Treisman, 1963) which states that the timing of intervals depends on a pacemaker generating pulses (like beats of a clock) and a signal accompanying the closing of a gait. The closing of the gait facilitates the gathering of pulses in an accumulator. Together, the pacemaker, the pulses, the gait, and the accumulator thus create an "internal clock". The number of collected pulses and the rate of their accumulation are translated into the duration of the "to-be-timed" interval and are transferred to working memory. The "calculated" duration is then compared to a time span similar to the reference memory. Finally, based on the comparison, a decision is made about the duration of the time span.

Biological mechanisms of time perception

Several interconnected brain regions, together comprising a network, have been implicated as biological substrates of the Scalar Expectancy model. In the model attention and memory play important roles. Attention facilitates proper counting of the generated pulses, and memory serves as a reference against which the timed intervals can be assessed (Gibbon, Malapanits, Dale, & Gallistep, 1997). The basal ganglia, with the aid of striatal dopaminergic transmission, play a role in the earliest stages of time perception to assess the duration of time intervals (Jones & Jahanshahi, 2011). The cerebellum is involved in the processing of intervals ranging from milliseconds to a second (Clarke, Ivry, Grinband, Roberts, & Shimizu, 1996), whereas time spans longer than a second are processed by prefrontal cortex with the aid of attention and working memory (Clarke et al., 1996; Mangels, Ivry, & Shimizu, 1998). Parietal and prefrontal cortices are thought to be involved in the indirect processing of time through attention and memory, and through the direct processing of time via cortico-striatal connectivity (Rao, Mayer, & Harrington, 2001; Üstün, Kale, & Çiçek, 2017). Since the interaction between frontal and mesolimbic regions and the role of basal ganglia in interval timing is mediated by dopaminergic connections (Jones & Jahanshahi, 2011), dopaminergic neurons in the basal ganglia have been proposed as the neural substrate of the "internal clock" of the Scalar Expectancy model. They are thought to facilitate the opening and closing of the gate of the accumulator, and to account for the rate of pulse accumulation (Allman & Meck, 2012).

The general principle of assessing time perception in an experimental setting is a subject's ability to correctly estimate or judge the duration of a certain time span. Focusing only on the

duration estimation leaves out the phenomenological experience of time but allows researchers to quantify any alterations in time perception across subjects and compare clinical and healthy groups. This sense of time can be measured by assessing the judgment of a given duration against clock time (Bschor et al., 2004). Most of the studies on altered time perception base their experiments and interpretations on the Scalar Expectancy Theory. Alterations in time perception are considered to be related to changes of the size and rate of pulse accumulation. The results are usually referred to as 'overestimation' or 'underestimation' (or lack thereof) of time intervals. Unfortunately, the studies I found (Bschor et al., 2004; Davalos, Kisley, & Ross, 2003; Schmidt, McFarland, Ahmed, McDonald, & Elliott, 2011; Tysk, 1990, 1984b; Wahl & Sieg, 1980) on objective time perception, as operationalized with the aid of time duration estimations, did not address the question of how a misperception of interval duration could be translated to the subjective experience of time. Thus, the existing literature about time estimation deficits does not address the question of how the experience of subjective time is brought about.

Psychological time

While healthy individuals exposed to boring or unpleasant events report that time seems to slow down (Zakay, 2014), the other way around our experience of time also affects the way we value events. An activity is usually evaluated as pleasurable and engaging when it seems to pass by quickly, but when we are told that the time it took was actually much longer, the same event may be valued as dull and irritating (Sackett, Meyvis, Nelson, Converse, & Sackett, 2010). Therefore, besides the direct mechanisms that determine our sense of time passing, cognitive functions are also involved in creating this effect. The same holds true for attention (Rao et al., 2001). As the famous "watched pot" phenomenon indicates, when one is explicitly attentive to the passage of time, one seems to experience every single passing second and may therefore feel that time goes unusually slow. Likewise, emotions contribute heavily to our subjective sense of time (for a review see, Lake, 2016). The anterior insula has been proposed as a "hub" facilitating the ultimate integration of such endogenous and exogenous cues (i.e. those from the body and the environment). Eventually this integration gives rise to the so-called "global emotional moment" (Craig, 2009) which unfolds in particular moments in time, thus creating the feeling of "now". Therefore, by integrating internal and external stimuli, the anterior insula creates an experience inherently associated with the subjective sense of time. Based on the salience of cues, emotions vary, and personal time varies with them. Thus, the "now" can be shortened or stretched out by high- and low-salience states, respectively. On the one hand, there is the objective clock time, which most humans can perceive, estimate, and reproduce fairly accurately. On the other hand, however, we have the subjective experience of "lived time" that operates beyond objective perception and is something very personal and fluctuating that can be difficult to tackle and quantify in the laboratory setting.

Time distortions in classifications of psychopathology

The traditional way to classify time distortions is to conceptualize them as on a par with other symptoms of disease, whether that be neurological disorder, mental illness, or intoxication state. Thus, they are usually grouped together with other perceptual distortions, hallucinations, depression, anxiety and headache, to mention some arbitrary examples at the phenomenological level, which are all thought to arise from some underlying disease process. By contrast, the work of Vogel et al. (2018) and Stanghellini et al. (2017) highlights that alterations of the perception of time can be conceptualized as the core of all other manifestations of MDD (and possibly also other psychiatric disorders). For that reason, the authors refer to MDD as "a disorder of lived time" and speculate that other symptoms of MDD are only mediated in the presence of its characteristic slowing-down of subjective time. This does not suggest that time distortions are causal factors for any of the other mental symptoms they co-occur with, after all time distortions can also occur without any additional symptoms. However, time distortions could be creating the conditions in which the otherwise vulnerable population develops other symptoms of disease. From the finding that our subjective sense of time determines to a large extent how we value our experiences in life (Sackett et al., 2010), it follows that the impact of time distortions on our perception of reality and self is probably profound. In this sense, personal time experience can be considered a crucial aspect of the way in which one connects oneself to the surrounding world. Time creates a structure whereby our experiences and feelings become integrated, and the sense of flow and causality ensues where the present is derived from the past and gives rise to the future. A fragmentation of this continuity is described by patients diagnosed with schizophrenia, where time is felt as a series of discrete snapshots rather than one continuous flow (Stanghellini et al., 2016; Vogel et al., 2019). Furthermore, during psychotic episodes, time may appear to fluctuate and alternate from slow-motion to quick-motion phenomena, whereas time is mostly decelerated in patients with depression. One might therefore speculate that fluctuations in subjective time may make one loose connection with reality, even to the point of the psychotic state, while a deceleration of subjective time facilitates a depressed mood. As for time structure fragmentation during the post-psychotic phase, it was found to be attributed to the inability of patients to link the present self to their past self, who had undergone the distressing experience of psychosis. As a consequence, these patients had difficulties incorporating their psychosis into their present, and therefore failed to have a healthy anticipation of the future (Vogel et al., 2019).

Notably, besides experiencing slow-motion phenomenon, many depressed patients also complain of the loss of their prior ability to experience emotions (Binswanger, 1960; Stanghellini et al., 2017; Tellenbach, 1980). This emphasizes the intertwined relationship of subjective time experience and emotions. Considering the role of the insula in the integration of emotions and our subjective sense of time, the distortion of both in depression might point to a common

neural deficit involving the insula. In this light it may be expected that when our sense of time gets distorted, the integration of our emotions may also become distorted, and that the same may hold true for the integration of other internal as well as external cues. Thus, time distortions appear to be capable of drastically affecting the synchronization of one's self with reality.

Limitations

Several limitations of this review need to be addressed. First, I was able to include and summarize a very limited number of papers. There were only four papers that properly classified reported time distortions as symptoms of AIWS. After an extensive search, I only found several additional papers that described subjective time alterations thoroughly enough to allow me to identify them as time distortions, even though the authors themselves sometimes used different names. Although time distortions are probably rare, I have reason to believe that they are also underreported due to a lack of awareness among clinicians and researchers. This may well be the reason why cases end up undiagnosed, misclassified, or unreported. Therefore, the cases I reviewed may not be representative of time distortions in general. Furthermore, in the literature reviewed here, I only found cases described in the context of neurologic or psychiatric conditions, whereas several studies indicate that in the general population, AIWS is more prevalent than traditionally thought. As a consequence, time distortions may also be more prevalent in the general population, without any associated pathology (Abe, Oda, Araki, & Igata, 1989; Shammas, 2020).

Conclusion

The 11 case reports and research papers that I reviewed indicate that time distortions are mainly reported in two forms, i.e. slow-motion and quick-motion phenomena, although structural alterations were also reported. None of them appear to be specific to any psychiatric or neurologic condition, although certain types appear to be more prevalent in the context of certain underlying conditions than others, such as the slow-motion phenomenon (or time deceleration) in depression, and structural changes of subjective time in the context of post-psychotic phase (Vogel et al., 2019). Since our sense of time forms the backbone of lived reality, distortions of time experience may have a profound effect on the experience of our reality and self. Thus, citing Vogel et al. (2018) and Stanghellini et al. (2017), I argue that time distortions may play a substantial role in the mediation of depressive and other psychopathological symptoms than traditionally assumed. A better understanding of their specific phenomenological aspects and neurobiological correlates may allow researchers and practitioners to enhance their understanding of these disorders, and to elucidate mechanisms of normal time experience.

Better Research Practices:

Own Your Research Decisions

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Most behavioural scientists have probably heard, at least once, that "social science isn't real science" (Berezow, 2012). Plagued by vague definitions and unquantifiable psychological concepts, unreplicable findings and a lack of generalisability and diversity, the psychological sciences have not enjoyed a stellar reputation in recent years. But what is 'real science'? What scientific methodology needs to be adopted to do good science? Some argue that the ultimate solution is to adopt an open science approach, meaning that researchers make their research practices transparent, share data and code and communicate with other researchers to come to the best possible understanding of the topic in question (e.g., Chambers, 2019; Jogalekar, 2013; Yong, 2012). However, due to the way in which publications and funding are rewarded at the moment, there is no real incentive to adopt an open science approach. Researchers have to constantly compete for funding, leading to a privatisation of resources. Some scientists do not want to share their data or code, worried that another researcher will win the grant they themselves have been fighting for with their sweat and tears. Journals further realise that their biggest profits will come from publishing exciting 'new' research that draws in large numbers of readers. After all, who is interested in reading the same studies over and over again? Any motivation for adopting open and honest good research practices thus seems to be shaded by the pressure for publications and funding. But there are reasons why adopting such practices can be rewarding after all. With this article we set out to help young researchers find the light, by showing why it is rewarding and necessary to learn about and adopt open science (OS) and good research practices (GRP) to do proper science. Here, we propose four crucial motivations to show that adopting open science practices can have an impact on the quality and relevance of the behavioural sciences.

The mumultifaceted landscape of open science.

Motivation 1: The replication crisis

As mentioned, an increasingly apparent issue within science, especially behavioural sciences, is an inability to reproduce results from earlier studies. This is especially alarming when non-replicable studies have been extremely influential in the field.

Take 'ego depletion,' for instance–a theory of self-control centered around the idea that willpower is limited, and once used up, needs to be replenished, like fuel in a tank. The first studies on this topic by Roy Baumeister and Dianne Tice at Case Western University set the stage for long research programs, hundreds of subsequent studies and millions of dollars in funding allocated to these ideas. However, when researchers took a closer look at the data, they found meta-analyses with strong biases (Hagger et al., 2010), that produced null results when reanalysed (Carter & McCullough, 2014). Furthermore, a replication attempt, with protocols vetted by the original authors, including Dr. Baumeister, found 'close-to-zero effects', despite involving 23 labs and almost 2000 participants (Hagger et al., 2016).

Ego depletion is a stark example of why psychology needs replication. Not only were years wasted on shaky research programs, but huge sums of (public) money were too. Moreover, the influence of these ideas were not limited to the scientific community, but spread widely amongst the general public. In 2011, Baumeister co-authored a best-seller popular science book, Willpower: Rediscovering the Greatest Human Strength. You may even find yourself applying this idea, telling yourself 'I did enough work, I need a Netflix break to refuel'. Recent research has even argued that taking an ego-depletion stance on will-power may hinder our self-control (Job et al., 2010). Had good research practices been applied sooner, time, public money and mental health could have been saved.

Another hyped, yet subsequently debunked finding is that of power-posing, led by Amy Cuddy, who has been branded the poster-child of the replication crisis[1]. Specifically, her work found that striking a powerful pose, like the 'Wonder Woman pose', characterised by hands on the hips, feet wide, and the head held high, led to participants feeling more confident, being more willing to take risks, and to a boost in testosterone and a decrease in cortisol, a hormone associated with stress (Carney et al, 2010). This research exploded–you may indeed have been one

1 See article by Susan Dominus, in New York Times Magazine: 'When the Revolution Came for Amy Cuddy'

of the 60 million viewers of her TED Talk. Yet, a 2015 replication with 200 participants found no evidence of changes in hormones or increases in risk taking.

Thus, replication—a core practice of good research—has allowed for the 'debunking' of some findings. The quest to create more reproducible research has been aided by adoption of preregistration, and methods like Bayesian statistics and computational modelling. With all these debunked studies, the outlook on science can sometimes seem bleak (see blogs by defeated social psychologists[2]). However, these replications are essential to move the field towards more robust findings, and force researchers to take a closer look at the mechanisms driving their results. Power poses, for example, may indeed boost self-confidence, but the mechanism behind this remains unclear. That this empirical crisis has come to light can be seen as a step forward for young psychologists, who certainly now have plenty of work to do. As scientists, we must commit to replicating past research in our own labs or as part of larger replication efforts[3], making sure our own new findings are robust by running multiple studies, and finally, being transparent about all our data and analyses by sharing these, when ethics and privacy permit. Replication is an essential good research practice, allowing for better science.

Motivation 2: Better theory

Reproducibility testing is a crucial part in the toolbox for better science. However, the confidence crisis goes beyond (ir)reproducibility of empirical studies. A sizable group of scientists argues that behavioural research suffers from a theory crisis (Oberauer & Lewandowsky, 2019).

The role of theory in psychological science is up for debate—whether it is meant to predict or explain behaviour. However, for either of these uses, we want theory to allow us to generalise our findings: if we do not have a theory that allows generalisation, we cannot transfer our existing scientific knowledge onto new cases that we want to predict or explain. The discourse on the theory crisis in behavioural research sheds light on problems with existing theory-making practices that make a concerning number of theories fail to robustly generalise (van Rooij, 2020).

Some of the key problems are an over-reliance on traditional statistical models, predictions being made by individual researchers rather than by theory itself, and a lack of cumulative theory-making. In contrast to fields such as biology or economics where researchers start from a rigorous (computational) description of the phenomena of concern and then suggest custom measurements, psychologists tend to fit phenomena into shapes dictated by traditional statistical models like ANOVA or linear regression (Borsboom, 2013). This cuts away all but the simplest—linear—associations from the complex behaviour and capacities of humans.

Formal or computational theories are greatly favoured by researchers concerned with the theory crisis in behavioural and cognitive research (Guest & Martin, 2020; Lee et al. 2019). Such theories entail mathematical description of how behavioural or cognitive data are generated, using, for example, differential equations. This not only allows a closer description of nonlinear processes specific to the phenomena, but it also automatically spits out predictions for different circumstances, obtained by simulating an equation with a change in any given variable in the equation. Computational theories thus allow us to build theory in a more transparent and precise way that depends less on individual researchers' reasoning and interpretations, and can more easily be built up together into complex, but more accurate, cumulative models of human behaviour and cognition.

Early career researchers who want to contribute to creating more transparent and reproducible theories may find one path in computational theories. Notably, this path does entail strengthening skills in programming and mathematics. The thought of running a computer simulation of empathic behaviour or psychedelic cognition hopefully sparks the motivation of some young researchers to acquire those skills.

Motivation 3: Science Communication and Citizen Science

The replication crisis is not just affecting researchers. With the rise of social media, 'fake news' and science-scepticism, public trust in science has eroded, which has become all too clear during the current pandemic. At the heart of this debate is 'science communication', which can refer to both the communication between researchers within the scientific community, as well as science 'outreach'—the practice of sharing scientific research with the public.

The process of informing and educating the public benefits researchers by generating interest and popularity in their work, which may in turn increase the number of citations in scientific journals (Ransohoff & Ransohoff, 2001; Phillips et al., 1991). However, this practice is currently flawed for a number of reasons. First, science communication is seen as part of the job of researchers, as put forward in 1985: "Learn to communicate with the public, [...] and consider it your duty" (The Royal Society 1985, p. 24). While many researchers may agree, in practice very few find the time to actively engage with society themselves, and leave the job to institutional PR professionals. Second, out of these popularisers, many may rely on sensationalism as a tool and focus on research results told as a form of success story, leading to a distorted view of scientific research (Gerber, 2014).

The Citizen Science movement aims to solve this problem of science outreach and to rebuild trust in science through the involve-

2 Michael Inzlicht, a researcher who worked on ego depletion, blogs about the replication crisis. See post 'Reckoning with the Past' on http://michaelinzlicht.com/
3 See 'Many Labs' replication efforts, involving dozens of researchers and labs working with the same methods to replicate findings.

ment of citizens (Gura, 2013, Kenens et al., 2020). Citizen science can take many forms. Most widely it involves data collection or analysis performed by amateurs or 'non-scientists' (Gura, 2013), but it can also be interpreted as the practice of generating hypotheses based on public interest or demand (PublicLab.org). Projects like the Extreme Citizen Science research group define it as "bottom-up practice that takes into account local needs, practices and culture" (Extreme Citizen Science (ExCiteS), 2020). Applications in research range from mapping and observing biodiversity (iNaturalist.org) to solving quantum physics problems (ScienceAtHome.org), often through the use of smartphone apps, websites or games. In neuroscience, citizens can participate in the quality control of large-scale MRI datasets by rating brain slices through a smartphone app (Keshavan, Yeatman & Rokem, 2019).

The benefit of citizen science is that the general public is intrinsically involved in the process and methods of research, rather than solely informed about the results. For scientists, especially psychologists, involving citizens in research through digital platforms can greatly increase the number of participants and thus permit statistically meaningful conclusions, aiding the reproducibility problem. Furthermore, with greater and more accessible outreach, the diversity in participants is increased, reducing bias and making research available for everyone.

By having the general public, amateur researchers or even schools (Dikker et al., 2017) participate in research, we as scientists can offer insight in the process and messiness of conducting scientific studies. This may lead to a more realistic and perhaps more critical view of scientific research among the general public the next time a headline about the brain "lighting up" comes across (i.e., Gueren, 2015). Thus, by involving the public in research we can address their questions more directly, make results available for a wider audience and rebuild trust and interest in research itself.

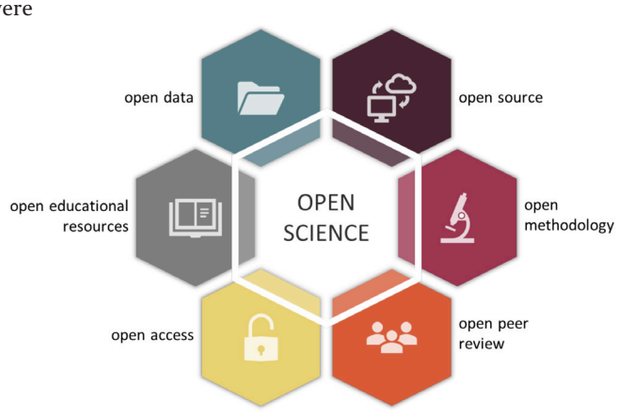
Moreover, citizen science can shift the paradigm of allocating research funds. The reason so few researchers engage in open communication, within the scientific community or outside of it, is because efforts to do so are barely recognised and funding and reputation is still largely based on metrics such as journal impact and citation scores (Benedictus, Miedema & Ferguson, 2016). Unified efforts from universities, journals and funders can shift this view to incorporate and reward efforts in communicating and engaging with the public and actively encourage the funding research proposals that employ citizen science.

Early career researchers can facilitate approaches in citizen science by choosing to work on or proposing these types of projects. However, longitudinally, we will have to rethink the way we currently study social phenomena under laboratory conditions with a small, biased sample size of first year psychology students, as discussed in the next section. As researchers, we can benefit from the amount and the multiple perspectives that a large, diverse dataset can bring. Yet ultimately, the motivation to engage in these projects should be to take scientific practice out of the lab and engage the public in science.

Motivation 4: Diversity

A final issue in science that we touch upon here is that of diversity and inclusion. As an initiative that seeks to make science more open, more accessible and collaborative, open science must also be more inclusive. As it stands, the majority of research is conducted by a few wealthy nations, with both researchers and participants often hailing from a specific class, race, and gender. By extension, this lack of diversity means that science is not as accessible to a diverse range of people. This creates a lack of accountability, which allows science to become boxed in by a limited perspective, and equally limited data, which can hardly be generalised on a world scale. This results in a specific world-view masquerading as objective truth, while in reality it is constrained by the researcher's background and sampling choices. In an APA blog post[4], Beth Azar gives the example of a visual perception study to illustrate this problem (Azar, 2010). In this 1966 study (Segar et al., 1966), it was observed that American students were more susceptible to certain visual illusions than students from other parts of the world, with some cultures appearing to be completely unaffected by these illusions. These visual illusions were often used to draw conclusions for the architecture and function of visual perception, universals of human nature that we purportedly share. Yet, this work was contingent on the sample selected, therefore ultimately unreliable and ungeneralisable.

Diversity should be an integral part of any open science initiative, especially when viewed through the lens of open science's foundational value of accessibility. For example, in 2018[5], one physics publisher, the Institute of Physics, divulged that most of their published work came from Northern American and Western European universities. Of those publications, men were overrepresented in terms of both authorship as well publishing positions, which means they were also the ones re-



An instance of Open Science principles

4 See 'Many Labs' replication efforts, involving dozens of researchers and labs working with the same methods to replicate findings.
5 This information can be found in the IOP's diversity report titled "Diversity and Inclusion in Peer Review at IOP Publishing"

sponsible for directing funding.

This overrepresentation in publication and positions of power in science must be addressed at the root – and every other level after that. First, entry into scientific fields must be made more accessible to a more diverse group of people. However, mere diversity without inclusion is not enough. Academic environments cannot only be conductive to entry for people from different backgrounds, but also help these individuals thrive. A more accessible and diverse environment will lead to reduced barriers of entry and promotion, as well as a more hospitable environment for different groups of people, as it would mean less bias in favour of one dominant group of people or less bias against marginalised people.

Moin Syed of the Open Science Foundation[6] further breaks the notion of diversity down into three principles, to make talking about diversity in science more concrete (Syed, 2020). The first of these is diversity in researchers. For this, Syed notes the importance of examining whether the environment, not only of science and academia, but of open science initiatives in particular, is open to and creates a safe space for marginalised communities, in addition to providing safe, accessible and equal entry points to people of different backgrounds.

The second principle is that of diversity of sampling. In a 2010 paper by Henrich et al., it was observed that 96% of psychological research samples came from Western industrialised rich developed nations, representing only 12% of the world's population, the so called WEIRD problem. Syed also notes, however, that this term cannot capture the scope of the problem fully as it doesn't include race, ethnicity and other dimensions of diversity that are also often ignored during sampling even within those WEIRD populations.

This leads to the third and final principle - that of diversity in perspectives. Syed explains that a diverse dataset needs to be examined through diverse perspectives to ensure equal treatment of participants and to combat implicit biases. More generally, even in different domains, a wide array of perspectives can ensure that cultural or other biases pertaining to the researcher's background do not affect the methodology and question formulation of the researcher. Regardless of the background of the researcher, they always need to consciously ensure their research does not operate within the cultural hegemonies of the mainstream - such as mistaking an optical illusion only seen in Westerners as a key to understanding the visual system of all humans.

These concepts are all intertwined. More diversity in the population of scientists would lead to a diversity of perspectives, and a diversity of data. However, all three dimensions can also be examined independently, and it's important to note that increasing diversity in one doesn't necessarily increase diversity in the other two categories. Instead, academia should maintain focus on all three of these, without excluding any particular one. To ensure diversity in science, we should be open to, and encourage admission of, scientists of diverse backgrounds and from all parts of the world. At the same time, we must closely examine and re-examine our own cultural biases and perspectives within the formulation of our research questions and methodology, while vigilantly maintaining a close eye on the kind of samples we take, ensuring increased diversity that will lead to more generalisable findings.

Conclusion

There are many problems in current behavioural research that need to be tackled to improve the reputation of the field. First, the ongoing replication crisis has eroded the fundament of good science. It is questionable how truthful current psychological theories really are. At the same time, others argue that the way in which we conceptualise psychological theories is flawed in itself. But not only research practices need to be improved. Research is far from approachable, having isolated itself from 'normal' society for centuries. The connection to people from outside of academia has been lost - even though the outcome of research is supposed to be for everyone. Finally, research is not inclusive and diverse, but is created by a specific group that only examines a specific sub-population.

For behavioural science to become more reliable, valid, generalisable and approachable something has to change. If the right actions are taken, the future of the field is not as brim as it seems. Researchers have it in their hands to change the course of the (behavioural) sciences. And a first start is easy. Simply starting to engage with other researchers, exchanging resources, knowledge and ideas, being open and more critical about others' and one's own work will come a long way. Open science might be the long sought-after solution to many problems that the behavioural sciences are currently facing. It will open doors to more communication and transparent research, simplifying the development of theories and enabling replicability. It will also encourage the involvement of citizens in the scientific process by opening the scientific discourse to the broad public. This will foster more inclusivity and diversity in science as well.

Check out the QR code for interesting resources to help you get started with open science. The **Open Science Initiative** at MBCS is a newly founded group of students who advocate better equipment of MBCS students to think critically about their research practices. Members of the initiative are pictured below. For more information or if you want to join the initiative, contact mbcs.openscience@gmail.com.

Annexes

References

6 Syed explains these concepts as part of a 2020 talk on diversity in open science. The script of his speech can be found on the OSF website.

Dissociating contributions of periodic and aperiodic neural activity in human visual working memory.

Quirine van Engen | **UC San Diego**

Ample evidence exists demonstrating the contributions of periodic, oscillatory neural activity to visual perception as well as working memory maintenance and recall. In particular, occipital alpha (8-12 Hz) and midline frontal theta (4-7 Hz) oscillations have been shown to parametrically track both the number of items held in working memory as well as successful recall. However, emerging evidence is showing the importance that aperiodic, non-oscillatory, neural activity plays in cognition and behavior. This aperiodic activity—which has been linked to contributions of postsynaptic excitation and inhibition—has a 1/f-like distribution in the neural power spectral density. Additionally, alterations in the aperiodic signal can be mistaken for event-related changes in oscillatory activity, even when no such changes to the oscillation necessarily need occur. Here, I examine to what degree well-described alpha and theta correlates of visual working memory are actually derived from oscillatory, as opposed to non-oscillatory aperiodic activity changes. To do this I reanalyzed EEG data from a visual working memory task (Adam et al., 2018) using an approach that quantifies both the aperiodic components of a power spectrum, as well as oscillatory power within a frequency band. First, I find that all 31 subjects in Experiment 1, and 38/45 of subjects in Experiment 2, show some degree of occipital alpha activity, while only 20/45 show some degree of midline frontal theta. This suggests that group-level analyses of midline frontal theta are more often than not measuring the aperiodic signal, and not actual oscillatory changes. In contrast, and in line with past work, there is a clear suppression of visual cortical alpha power, with more suppression with increasing memory load. In addition, there was also an effect of memory load on both the aperiodic exponent and offset. Higher set-sizes correspond to "flatter" spectral slopes than lower set-sizes, driven by a general decrease in power of lower frequencies with a simultaneous increase in higher frequencies. Surprisingly, past work shows that midline frontal theta power is correlated to good performance. Here, using the same data, I show a decrease in absolute theta power for both good and poor performance during the retention period, compared to baseline, driven by the aperiodic offset. However, theta power relative to the aperiodic signal did not differ between good and poor performance. Therefore, I find that the aperiodic signal better explains the data than oscillatory power, which is in contrast with the assumption of previous research that assumes absolute theta power is equivalent to oscillatory power. Thus, narrowband filtering always filters both oscillatory theta power and the aperiodic signal, but cannot disentangle them, which can lead to misinterpretations of the neural activity change.

1 - Introduction

1.1 - Frontal theta power has been correlated to working memory performance

The invention of electroencephalography (EEG) made it possible to noninvasively measure neuronal responses (Berger, 1929). These neuronal responses can be defined into two components. 1) The periodic, oscillatory activity, and; 2) the aperiodic, non-oscillatory activity (Buzsáki et al., 2012). The periodic component is often described by canonical frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), low gamma (30-60 Hz), and high gamma (60-250 Hz). Each of these frequency bands are linked to different aspects of cognition, attention and behavior (Frey et al., 2015; Herrmann et al., 2016; Klimesch, 1999; Sadaghiani & Kleinschmidt, 2016). For instance, midline frontal theta power has been correlated with working memory performance for more than a decade. According to a review, there is a tonic decrease in theta power, paired with a phasic increase that is related to good performance (Klimesch, 1999). Furthermore, theta band activity increases when more items have to be held in memory (Brzezicka et al., 2015; Jensen & Tesche, 2002). And theta power for good performance is higher than poor performance during memory maintenance of information (Adam et al., 2015, 2018). Newer research also tries to find a causal link between frontal theta power and working memory, demonstrated by 4 Hz tACS leading to an increase in working memory capacity. Whereas 7 Hz stimulation did not alter working memory capacity (Bender et al., 2019). Thus,

midline frontal theta power has been extensively researched in relation to working memory.

1.2 — The aperiodic signal contains crucial information

The aperiodic signal is far less studied than canonical frequency bands. This signal can be derived from a power spectrum of electrophysiological data, and can be described as a 1/f-like (pink) noise (He, 2015). It is characterized by two components, an exponent and an offset. One of the first researchers investigating the aperiodic components collected resting state EEG from participants in an eyes-open or eyes-closed condition (Pritchard, 1992). The aperiodic signal can be described by the formula:

$$Power = 1/(Frequency)^{\chi}$$

Where χ is what will be referred to throughout as the aperiodic exponent, although previous research has labeled it as 'N' or 'β' (Colombo et al., 2019; Lombardi et al., 2017; Wen & Liu, 2016). If $\chi = 0$, the power spectrum is flat and the signal is traditionally described as "white noise". If $\chi = 1$, the power spectrum is truly 1/f and the signal is described as "pink noise". And if $\chi = 2$, the power spectrum is steeper, which means that compared to "pink noise", the lower frequencies have relatively more power, and the higher frequencies have less power. This can be described as "brown noise" (Pritchard, 1992).

Furthermore, there are hints that the aperiodic exponent is related to the excitation/inhibition balance (E:I) in the brain. This has been suggested by Gao et al. (2017), who designed a computational model to infer the E:I ratio from the power law exponent derived from electrophysiological power spectrum from both rat and macaque recordings. They found in simulation and in empirical data that the exponent is related to the E:I ratio. Another example comes from Lombardi et al. (2017), who tested different E:I ratios in a model for neural avalanches. Having a higher proportion of inhibition reduces the probability of neuronal avalanches to occur. These neuronal avalanches could be related to LFP data, and thus to the exponent of a power spectrum (He, 2015). What is interesting is that the exponent found by Lombardi et al. (2017), a computational study, is similar to the exponent of previous research in which EEG was measured from human participants (Pritchard, 1992). But this was only true when the proportion of inhibition to excitation was 0.3, which they argue is in accordance with experimental findings.

Moreover, several labs have concluded that the aperiodic signal is strongly related to aging. First, Voytek et al. (2015) shows with EEG and a visual working memory task that older adults have flatter power spectra than younger adults. From that same paper, this finding also holds true for ECoG in epileptic patients who performed auditory tasks. Second, Dave et al. (2018) got similar results as the previously described research, but when subjects performed a lexical prediction task. This flattening in power spectrum over age is suggested to be correlated to cognitive decline in general and does not seem to be task-specific. In addition, the exponent has also been linked to clinical relevance (Leemburg et al., 2018; Peterson et al., 2017). For instance, the power spectra are steeper for rats that underwent surgery that induces a stroke than those for rats that underwent sham surgery. The exponents normalized after 30 days of recovery. The researchers argue that targeting the aperiodic components of the power spectrum might work more efficiently than enhancing or suppressing specific frequency bands for improving stroke recovery (Leemburg et al., 2018). Furthermore, schizophrenia used to be characterized by disrupted oscillations. However, research shows that the aperiodic signal is a better predictor for schizophrenia than individual oscillatory frequency bands (Peterson et al., 2017). Lastly, Colombo et al. (2019) investigated the relationship between the aperiodic exponent and consciousness. They conclude that a steeper power spectrum during resting state EEG, e.g. a higher aperiodic exponent, is a reliable marker for unconsciousness in anesthesia.

Even though it has been shown that the aperiodic component contains crucial information (Dave et al., 2018; Gao et al., 2017; He, 2015; Leemburg et al., 2018; Lombardi et al., 2017; Peterson et al., 2017; Pritchard, 1992; Voytek et al., 2015), most researches ignore this in their analysis. Rather, researchers typically pre-select one or more canonical frequency bands of interest based on previous research, and focus analyses on those bands. Then, the data is band-pass filtered in the time-domain within the limits of the frequency band. This is followed by a Hilbert transform that calculates the power within the frequency band. This method is problematic, however, because: 1) The absolute power is filtered, thus no distinction can be made between oscillatory activity and the aperiodic signal; 2) Filtering can lead to the appearance of oscillations, even when none are truly present, and; 3) Due to task demands or age effects, there could be a shift in center frequency that causes the oscillation to slide outside of the filtering window for one group or one condition, but not the other. Resulting in the appearance of a change in activity (Figure 1). But most importantly, it is assumed that all participants exhibit oscillatory activity, while this may not be the case.

Besides, it is vital to avoid methodological monism because the brain is a complex system that uses different functional mechanisms (Roberts et al., 2015). The aperiodic signal is independent of the oscillatory activity within frequency bands (Pritchard, 1992). For these reasons, our goal is to reanalyze classical results, using an alternative approach that separates the oscillatory activity from the aperiodic signal, so that both can be analyzed individually.

1.3 — Investigate the aperiodic signal and periodic activity separately in relation to working memory capacity

Even though researchers have recently shown more interest in the aperiodic signal, it has yet to be studied in relation to cognitive functions, such as working memory. That is why for this research I will use EEG and behavioral data from a visual working memory task (Adam et al., 2018) to separate oscillatory activity from the

aperiodic signal to investigate them independently, and relate them to the original results . For this, a model called FOOOF (fitting oscillations & one-over f) (Haller et al., 2018) will be used. This model is able to fit the aperiodic signal of a power spectrum and extract peaks of oscillatory activity. These peaks are characterized as "bumps" on top of the aperiodic signal (Haller et al., 2018; He, 2015).

The visual working memory task is based on Vogel & Machizawa, (2004), in which they show that the contralateral delay activity (CDA; contralateral minus ipsilateral) scales with working memory load and correlates with individual working memory capacity. Adam et al. (2018) replicated these results, and further investigates alpha and theta power to working memory capacity. In experiment 1, in line with previous research (Adam et al., 2015), they conclude that lateralized alpha power is more suppressed during memory maintenance of higher set-sizes than smaller set-sizes. Furthermore, they use a new set of participants in experiment 2 and keep the set-size at six items. Now, they are able to discriminate

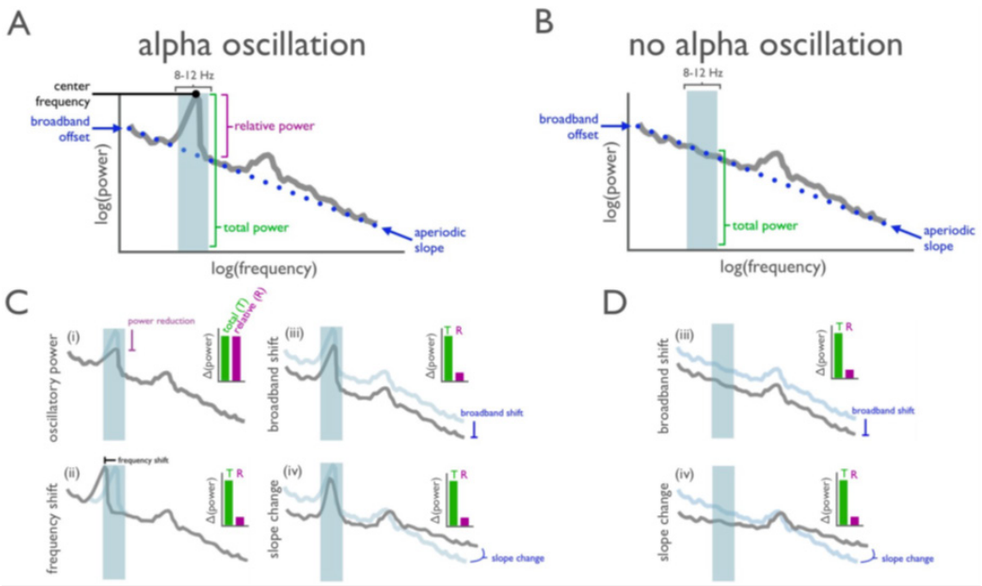


Figure 1: Adapted from (Haller et al., 2018). When looking at a power spectrum, there are multiple reasons for finding differences in absolute power in a frequency range that cannot be explained by oscillatory activity. All power spectra are shown in a log-log scale. A) A power spectrum shows the aperiodic fit by the exponent (slope) and offset, and the bump is oscillatory alpha activity (between 8 and 12 Hz). The bump is described as relative power, which is the total power minus the value of the aperiodic fit. B) Example of a situation when there is no oscillatory alpha activity. However, there is still power whiting the frequency range due to the aperiodic fit. C) Four different reasons for finding a change in absolute power. (i) Shows a true reduction in oscillatory power. (ii) Shows that the peak shifts out of the frequency range and is thus measured as a reduction when using basic filtering and the Hilbert transform. (iii) A shift in the aperiodic offset could also induce a seemingly difference in power, but this is not due to a change in oscillatory activity. (iv) A change in the exponent reduces the power in lower frequencies and increases the power in higher frequencies. Note that the relative power does not change. D) Another example of a shift in the offset or exponent. This figure shows the importance of incorporating the aperiodic components of the data to be able to draw conclusions about oscillatory activity.

between trials with good or poor performance within participants. In contrast with the previous paper, they do not find a significant difference between performance for lateralized alpha power. However, midline frontal theta power does predict performance.

First, based on the results of Adam et al. (2018), I hypothesize that there will be an interaction effect between hemisphere and set-size on relative alpha power. Since this is exploratory research into the aperiodic signal, no hypothesis is made regarding the aperiodic signal. Second, they did not find statistical difference in lateralized occipital alpha power between good or poor performance, which was unexpected (Adam et al., 2015). I hypothesize that the difference in absolute alpha power suppression due to performance might be hidden by a combination of relative alpha power and a shift in the aperiodic signal. Third, based on other research (Dave et al., 2018; Voytek et al., 2015; Waschke et al., 2017), I hypothesize that the effect of performance on midline frontal theta power might be driven not solely by oscillatory activity, but also by event-related changes in the aperiodic signal.

2 - Method

2.1 - Study design from Adam et al., 2018

2.1.1 - Participants

Different participants were recruited for experiment 1 and 2. The difference between the two experiments is the set-sizes. In experiment 1, the set-size varied between one, three or six items, and in experiment 2, the set-size was kept at six items. 31 participants were included in experiment 1, and 48 participants in experiment 2. After artifact rejection and checking for sufficient trials per condition (75 trials in experiment 1 and 40 trials in experiment 2), 29 participants remained in experiment 1, and 38 in experiment 2 for further analyses.

2.1.2 - Task design

Participants performed a modified version of a change detection task (Vogel & Machizawa, 2004), in which they were asked to

fixate in the middle of the screen at all time, except during the response. A cue was presented for 1100 ms to indicate whether they had to memorize the colors of the squares on the right or the left side of the screen. The memory array was presented for 250 ms. Afterwards, there was a retention period for 1300 ms, after which a response for each square had to be given (Figure 2). The number of squares were equal on each side so that each hemisphere had the same visual input. This was to ensure that hemispheric differences in neural activity were most driven by cognitive demands, rather than perceptual demands. Each block consisted of 30 trials. For experiment 1, each block had 10 trials for each set-size, and experiment 2 contained 30 trials of set-size six.

2.1.3 - EEG measurements

An EEG set up from ElectroCap International (Eaton, OH) was used for the recoding. This cap contains 20 electrodes according to the 10/20 international sites. In addition, electrooculography (EOG) was recorded to measure horizontal eye movements and blinks. Two additional electrodes were placed on the occipital lobe: OL was placed between T5 and O1, and OR was placed between T6 and O2.

2.2 - Replicating the original results

2.2.1 - EEG artifact rejection and pre-processing

Trials that included horizontal eye movements, eye blinks or excessive noise were removed. For full details, see the original paper (Adam et al., 2018). In their data, they included an array of indices of trials that have to be excluded based on their criteria. These arrays are used for trial rejection for both experiments. Furthermore, the EEG data was already down-sampled to 250 Hz.

Electrodes of interest are left occipital and parietal electrodes (O1, OL, P3, PO3 and T5), and right occipital and parietal electrodes (O2, OR, P4, PO4 and T6). These groups were used to compute lateralized alpha power in experiments 1 and 2. Midline frontal electrodes (F3, F4 and Fz) were used for theta power in experiment 2.

2.2.2 - Time-frequency analysis and statistical analysis

For traditional time-frequency analyses, the time-series were filtered using a bandpass filter. Theta power was filtered between 4 and 7 Hz, and alpha power between 8 and 12 Hz. Then, the data was baselined on the period before the cue (400 ms). The midline frontal electrodes were used to analyze theta power for experiment 2. For lateralized alpha power, the power of the ipsilateral electrodes were subtracted from the contralateral electrodes for both experiments 1 and 2.

Trials were averaged per condition and per participant, and the overall signal per condition was averaged for the duration of the retention period (400 – 1500 ms). Then, a two-way repeated-measures ANOVA was performed to test for statistical differences between the hemispheres and set-sizes of experiment 1 on alpha power. For experiment 2, a two-way repeated-measures ANOVA was used for the effect of performance and hemisphere on alpha power. Lastly, a pairwise t-test was used to test the statistical difference between good and poor performance on midline frontal theta power.

2.3 - New approach: Separating oscillatory activity from the aperiodic signal

2.3.1 - The FOOOF model

A power spectrum consists of an aperiodic component and oscillatory activity that can be described using the formulation:

$$P = L + \sum_{n=0}^{N} G_n$$

P is the power spectrum, L is the aperiodic signal and G_n is a Gaussian fit to a peak in the spectrum that is defined as oscillatory

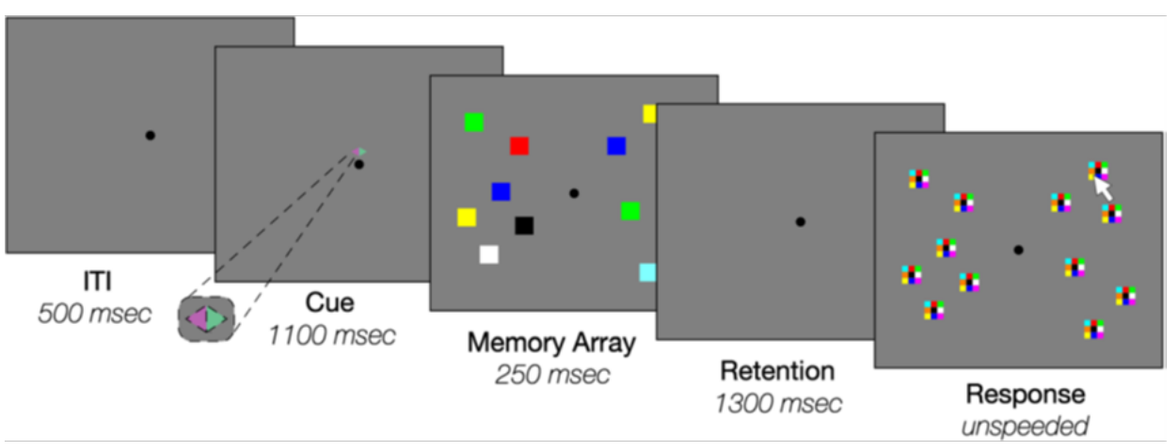


Figure 2: Example of a trial in experiment 1 and 2. Adopted from Adam et al., (2018). Participants are asked to fixate in the middle of the screen during the whole length of a trial. After 500 ms of fixating, a cue appears on the screen indicating which side to attend to. After this cue is presented for 1100 ms, the memory array appears for 250 ms with cubes on each side of the screen to keep the visual input for both hemispheres equal. Then participants have to remember the color of each cube for 1300 ms during the retention window. After which a response has to be given for each cube individually.

activity. For the aperiodic fit, the following formula is used:

$$L = b - \log(k + F^{\chi})$$

The aperiodic signal consists of the parameters b, k and χ. b is the offset, k is the knee, χ is the exponent and F is the input frequencies. Then to determine if a peak is present, a Gaussian fit is used in the following form:

$$G_n = a * \exp\left(\frac{-(F-c)^2}{2 * w^2}\right)$$

The parameters of the peak are a, c and w. a is the amplitude of the peak, relative to the aperiodic fit, c is the center frequency, w is the width and F is the input frequencies.

The model works by first estimating the aperiodic fit which is then removed from the power spectrum in a semi-log space. Second, Gaussians are iteratively fit and removed from the spectrum. Third, the multi-Gaussian fit is removed from the original spectrum to re-fit the aperiodic fit. Model goodness is measured in explained variance or the error between the fit and the original power spectrum (Figure 3). Full details of the model can be found in this paper: (Haller et al., 2018).

2.3.2 - Include participants that exhibit oscillatory activity

Another inclusion criterion was introduced before analyzing participants beyond the previous report: participants had to exhibit some degree of oscillatory activity within the theta or alpha frequency range, depending on the experiment and electrode group. Thus, for alpha power in experiment 1 and 2, participants were checked for a peak between 8 and 12 Hz on the occipital/parietal channels. And for theta power during experiment 2, participants were checked for a peak between 4 and 7 Hz that was distinct from alpha activity on midline frontal channels. To check this, a power spectrum was generated for every trial, for the whole trial length with Welch's method and a Hanning window of two times the sampling frequency (2*250 samples). The model was applied to the power spectrum in the frequency range of 2- 40 Hz. The FOOOF algorithm requires certain settings to fit individual datasets (for a full description of the model settings, see details in (Haller et al., 2018)). For this analysis, I set the limits of the width of the peaks that can be fit to a minimum of 2 Hz and a maximum of 8 Hz, since a smaller bandwidth might induce overfitting of peaks that are actually wider. Also, to prevent overfitting of relatively flat spectra without peaks, FOOOF requires amplitude threshold for determining the height of the bump, relative to the aperiodic signal, to be considered a peak. This threshold was set at 0.2 μV2/Hz for the alpha frequency band, and 0.1 μV2/Hz for theta frequency band. Different absolute thresholds were chosen, since theta power is typically lower than alpha power, relative to the aperiodic fit. I manually checked these settings for alpha power. For both experiments, FOOOF successfully discriminated between participants who exhibited alpha power and those who did not. However, discriminating participants based on theta power proved to be more difficult. Not all participants exhibited a distinct theta peak. A portion of participants also exhibited alpha power on the frontal electrodes that bled into the theta frequency range. Therefore, determining whether a participant exhibits theta power was guided by FOOOF and confirmed with manual classification. The resulting theta versus no-theta groups can be seen by comparing Figures 7&8.

2.3.3 - Generating single trial power spectra and applying FOOOF

A power spectrum was created for each trial, averaged over either the contralateral occipital/parietal electrodes, the ipsilateral occipital/parietal electrodes, or the midline frontal electrodes. The same electrodes were used as in the replication results. A time window from 400 to 1500 ms after memory array onset (1100 ms) was used for the retention period to calculate the power spectra, excluding the early perceptual ERP time points. An 800 ms time window from -1900 ms to -1100 ms before cue onset was used for the baseline period. Because this time window was smaller than the retention time window, zero-padding was used at the beginning and end to ensure that both time periods have an equal amount of time points. Power spectra were created with a Hanning window with a window that was equal to the length of the data (275 time points = 1100 ms). Note that the time-window for calculating the absolute power for the replicated results is the same as generating a power spectrum to use in this approach.

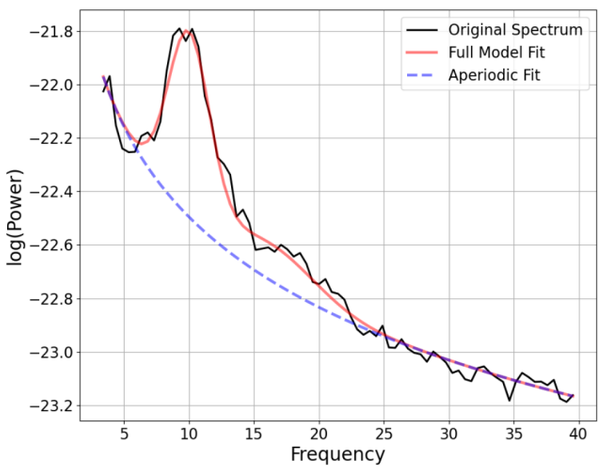


Figure 3: Example of an aperiodic fit and full model fit from FOOOF. The graph is presented in a semi-log space in which power is in log space. The black line is the original power spectrum, the blue dotted line represents the aperiodic fit and the red line represents the full model fit, which consists of the Gaussian fits and the aperiodic fit.

The model was applied to these power spectra using the same settings described in section 2.2.3. Then, four outputs are collected. 1) The relative power within a frequency range of 8 to 12 Hz for alpha power and 4 to 7 Hz for theta power, for both the retention period and baseline period. If a peak was absent, the power was considered "0"; 2) The center frequency of the alpha or theta peaks. If a peak was absent in either the retention period or the baseline period, there cannot be a center frequency. Any trial lacking a peak was excluded from the analysis; 3) The aperiodic exponent; 4) The aperiodic offset. A baseline correction was performed by subtracting the baseline values from the values

during the retention period in a trial-by-trial fashion for all four outputs. Afterwards, each output was averaged per condition.

2.4 - Statistical analysis

A two-way repeated measures ANOVA was applied to the alpha frequency band for to examine the effect of hemisphere and set-size in experiment 1, or performance in experiment 2 on the four outputs, relative power, center frequency, aperiodic exponent and aperiodic offset. Additionally for experiment 1, a pairwise t-test with Bonferroni correction was applied as a post-hoc test to examine the differences between the three set-sizes. Furthermore, a pairwise t-test was used to examine the differences in performance on the theta frequency band for experiment 2.

In addition, a one-sample t-test was performed on each output per condition to see if it was significantly increased or decreased from baseline. This was done by testing the baselined outputs against a mean of zero.

2.5 - Software

All data was processed with the Python programming language (version 3.7.1). Signal processing was done with the NeuroDSP module (version 1.0.0) (Cole et al., 2019), and power spectra were fit with the FOOOF toolbox (version 0.3.1) (Haller et al., 2018). All statistics were performed in JASP (version 0.9.2.0), and plots were created using Matplotlib (version 3.0.2).

3 - Results

3.1 - Replicated results using a time-frequency analysis

3.1.1 - Participants

For experiment 1, 31 participants were recorded. Adam et al. (2018) rejected two participants who had fewer than 75 trials per condition (set-size 1, 3 or 6). Here, I rejected four participants, based on the same exclusion criteria, leaving 27 participants for the analysis. For experiment 2, 48 participants were recorded, but three had missing data and were excluded. Furthermore, seven participants were rejected who had fewer than 40 trials per condition (good or poor performance). Thus, 38 participants were included in this analysis.

3.1.2 - Lateralized occipital alpha power correlates with set-size and performance

The assumption for sphericity was violated for the set-sizes and interaction effect, thus the Greenhouse-Geisser correction was used. I found that occipital alpha power differs per set-size during the retention period ($F(1.3, 33.7) = 8.184$, $p = 0.004$, $\eta^2 = 0.332$). The post-hoc analysis with a Bonferroni correction shows that alpha power for set-size 6 ($\mu = 1.901 \pm 1.969$) is significantly different from set-size 3 ($\mu = -1.644 \pm 1.853$) ($t(26) = 3.134$, $p = 0.013$, $d = 0.603$) and set-size 1 ($\mu = -1.267 \pm 1.444$) ($t(26) = 3.338$, $p = 0.008$, $d = 0.642$). Furthermore, contralateral alpha power ($\mu = -1.733 \pm 1.723$) was significantly lower than ipsilateral alpha power ($\mu = -1.474 \pm 1.79$) ($F(1, 26) = 2.706$, $p = 0.001$, $\eta^2 = 0.332$). Unlike the results from the original paper **(Figure 4A)**, I found no interaction effect between set-size and hemisphere ($F(1.5, 39.3) = 2.861$, $p = 0.082$, $\eta^2 = 0.099$). However, I do find a similar trend in the data **(Figure 4D)**.

When looking at the difference in alpha power on the performance when the set-size is kept constant at six items (experiment 2), I saw a similar effect, but on performance. Like the results from the original paper (Figure 4B), alpha power during trials where a participant performed good ($\mu = -1.288 \pm 2.154$) was lower than on poor performance trials ($\mu = -1.046 \pm 1.829$) ($F(1, 37) = 2.221$, $p = 0.019$, $\eta^2 = 0.139$). Furthermore, there was a main effect of hemisphere ($F(1, 37) = 2.742$, $p < 0.001$, $\eta^2 = 0.317$), wherein the contralateral side ($\mu = -1.302 \pm 2.14$) had less alpha power than the ipsilateral side ($\mu = -1.033 \pm 1.843$). However, an interaction effect between performance and hemisphere was not statistically reliable ($F(1, 37) = 3.928$, $p = 0.055$, $\eta^2 = 0.096$) **(Figure 4E)**.

3.1.3 - Midline frontal theta power predicts performance

According to the original study (Adam et al., 2018), midline frontal theta power predicts performance, both during the retention period, as well as during the cue period (500 ms before memory array onset) **(Figure 4C)**. The replicated results show that good performance ($\mu = -0.101 \pm 0.385$) had more theta power than poor performance ($\mu = -0.255 \pm 0.382$) during the retention period ($t(37) = 3.371$, $p = 0.002$, $\eta^2 = 0.547$) **(Figure 4F)**.

3.2 Results after separating oscillatory activity from the aperiodic signal

3.2.1 Participants

For this analysis, only participants that exhibit alpha or theta power were included. This was checked by averaging the power spectra from all trials. Power in a specific frequency band was considered present if the relative power (absolute power minus the aperiodic fit) exceeded an absolute threshold set at 0.2 μV2/Hz for alpha power and 0.1 μV2/Hz for theta power. Interestingly, all 31 participants in experiment 1 exhibited alpha power according to these criteria. Seven out of 45 participants in experiment 2 did not exhibit alpha power, and only 20 out of 45 participants exhibited theta power **(Table 1)**. After rejecting participants on the same criteria as for the replicated results, there were 27 participants included in experiment 1, 31 participants in experiment 2 for alpha power, and 17 in experiment 2 for theta power.

Furthermore, since the participants were almost divided in half based on theta power, I decided to also analyze the group that did not exhibit theta power ($n = 21$) to see if there is a difference in the aperiodic components.

3.2.2 Experiment 1 – set-sizes

In experiment 1, the set-size varied between one, three and six items. For each of those set-sizes and the hemispheres, the four outputs of FOOOF were collected. Each trial was baselined by subtracting the FOOOF outputs of the baseline period (before the cue onset) from the retention period. Figure 5A&B show the power spectra and the aperiodic signal of the different set-sizes and the baseline, respectively. The baseline is averaged over all the conditions (set-sizes and sides). The set-sizes are averaged over ipsi- and contralateral electrode groups. Furthermore, Figure 5C&D shows the averages of the four outputs, relative power, center frequency, aperiodic exponent and offset for the periodic and aperiodic components.

First, a two-way repeated-measures ANOVA shows a significant main effect of hemisphere ($F(1,26) = 15.752$, $p < 0.001$, $\eta^2 = 0.377$) on relative alpha power, and a trend for set-size ($F(1.5, 38.9) = 3.396$, $p = 0.056$, $\eta^2 = 0.116$). No interaction effect was found between set-size and hemisphere for relative alpha power. Only relative alpha power for set-size 6 on the contralateral hemisphere was significantly lower than baseline ($t(26) = -2.293$, $p = 0.03$, $\eta^2 = -0.441$).

Second, a significant main effect of set-size was found for center frequency ($F(1. 4, 35.7) = 5.043$, $p = 0.021$, $\eta^2 = 0.162$) and for hemisphere ($F(1, 26) = 12.21$, $p = 0.002$, $\eta^2 = 0.32$). However, the post-hoc test for set-size shows no significance between the set-sizes suggesting that no pairwise effect exists, just the overall parametric effect. There was also an interaction effect between hemisphere and performance ($F(2, 52) = 3.692$, $p = 0.032$, $\eta^2 = 0.124$). The only conditions in which the center frequency was significantly different from baseline was on the contralateral hemisphere for both set-size 3 and 6 ($p < 0.05$).

Table 1. Overview of participant selection per experiment and frequency band (rows). Also showing the group size for further analysis.

	PARTICIPANTS	COMPLETED	WITH OSCILLATORY ACTIVITY	TOTAL INCLUDED
EXPERIMENT 1 - ALPHA	31	31	31	27
EXPERIMENT 2 - ALPHA	48	45	38	31
EXPERIMENT 2 - THETA	48	45	20	17

Third, I found that the exponent was significantly different per set-size ($F(2,26) = 15.258$, $p < 0.001$, $\eta^2 = 0.37$). Set-size 6 was flatter than set-size 1 ($t(26) = 5.602$, $p < 0.001$) and set-size 3 ($t(26) = 3.624$, $p < 0.001$). Furthermore, the only condition that was not significantly decreases was for the contralateral hemisphere, set-size 1 (set-size 1 and 3, $p < 0.05$. Set-size 6, $p < 0.001$).

Fourth, there was also a main effect of set-size on the aperiodic offset ($F(2.26) = 15.972$, $p < 0.001$, $\eta^2 = 0.381$). Set-size 6 was higher than set-size 1 ($t(26) = 5.312$, $p < 0.001$) and set-size 3 ($t(26) = 4.268$, $p < 0.001$). No effect of hemisphere, nor interaction effect was found for the aperiodic offset. The aperiodic offset was significantly lower for all conditions during the retention period, compared to the baseline ($p < 0.001$).

3.3 Experiment 2 – good vs. poor performance

3.3.1 Lateralized alpha power

In experiment 2, the set-size was kept at six items. Good performance was defined as having more than three correct responses on a trial; poor performance was having fewer than three cor-

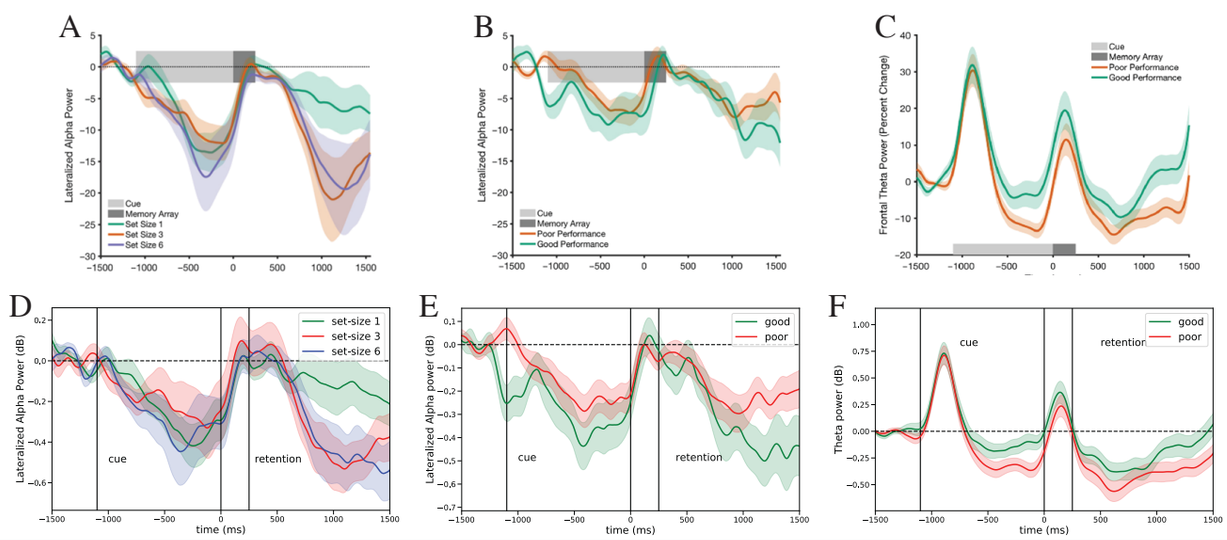


Figure 4: The trend of the original results were replicated. Percent change (A, B, C) or the absolute power (D, E, F) was calculated over time for alpha or theta power. Alpha power was lateralized by subtracting the ipsilateral power from the contralateral power. Each trial was baselined on the period before the cue onset (-1500 to -1100 ms) and analyses were performed on the retention period (400 to 1500 ms).The top row (A, B, C) are figures adapted from Adam et al. (2018). A) Shows that lateralized alpha power is significantly lower for set-size 3 and 6, than for set-size 1. B) No statistical significance is found for lateralized alpha power between good and poor performance. C) Theta power is higher for good performance than poor performance during the retention period. The bottom row (D, E, F) are the replicated results. The solid line represents the grand average, and the shaded error bars represent the SEM. All three figures resemble the original results. However, even though the trend is similar, lateralized alpha power was not significantly different between set-sizes (D).

rect responses. For both hemispheres and both performances, the four outputs of FOOOF were collected. Each trial was baselined by subtracting the FOOOF outputs of the baseline period (before the cue onset) from the retention period. Figure 6A&B show the power spectra and aperiodic signal of good and poor performance and the baseline. The baseline is averaged over all conditions (performance and hemisphere). The good and poor performance are averaged over ipsi- and contralateral. Furthermore, Figure 6C&D show the averages of the periodic signal, relative power and center frequency, and the aperiodic components, exponent and offset.

First, a two-way repeated-measures ANOVA shows an effect of performance on alpha power ($F(1,30) = 4.722$, $p = 0.038$, $\eta^2 = 0.136$). The relative alpha power during poor trials was higher than during good trials. Furthermore, there was also an effect of hemisphere ($F(1,30) = 9.440$, $p = 0.004$, $\eta^2 = 0.239$) in which contralateral had less alpha power than ipsilateral. No interaction effect was found between the performance and hemisphere ($F(1, 30) = 3.843$, $p = 0.059$, $\eta^2 = 0.114$). Only alpha power on the contralateral hemisphere during good performance was significantly lower compared to baseline ($t(30) = -2.172$, $p = 0.038$, $d = -0.39$).

Second, there was an effect of performance on alpha center frequency ($F(1,30) = 4.572$, $p = 0.041$, $\eta^2 = 0.132$), and a difference in center frequency on hemisphere ($F(1,30) = 8.485$, $p = 0.007$, $\eta^2 = 0.22$). Alpha center frequency on the contralateral hemisphere during good performance was significantly lower compared to baseline ($t(30) = -2.704$, $p = 0.011$, $d = -0.486$).

Third, no statistical differences were found for the aperiodic exponent or offset. However, the offset was significantly lower than baseline for all conditions ($p < 0.05$).

3.3.2 Midline frontal theta power – group that exhibits theta power

Figure 7A&B show the power spectra and aperiodic signal of good and poor performance and the baseline measured on the midline frontal electrodes. The baseline is averaged over good and poor performance. Figure 7C&D show the averages of the periodic signal, relative power and center frequency, and the aperiodic components, exponent and offset.

There is no difference in relative theta power between good and poor performance, nor is this different from baseline. No significant differences were found in the center frequency, or in the aperiodic components between good and poor performance. Only the aperiodic offset was significantly reduced from baseline for both good ($W = 12$, $p = 0.001$, $d = -0.843$) and poor performance ($W = 14$, $p = 0.002$, $d = -0.817$).

3.3.3 Midline frontal theta power – group that does not exhibit theta power

The power spectra of the group that does not exhibit relative theta power is shown in Figure 8A, and the aperiodic signal in Figure 8B. None of the FOOOF outputs were statistically different between good and poor performance after baseline subtraction

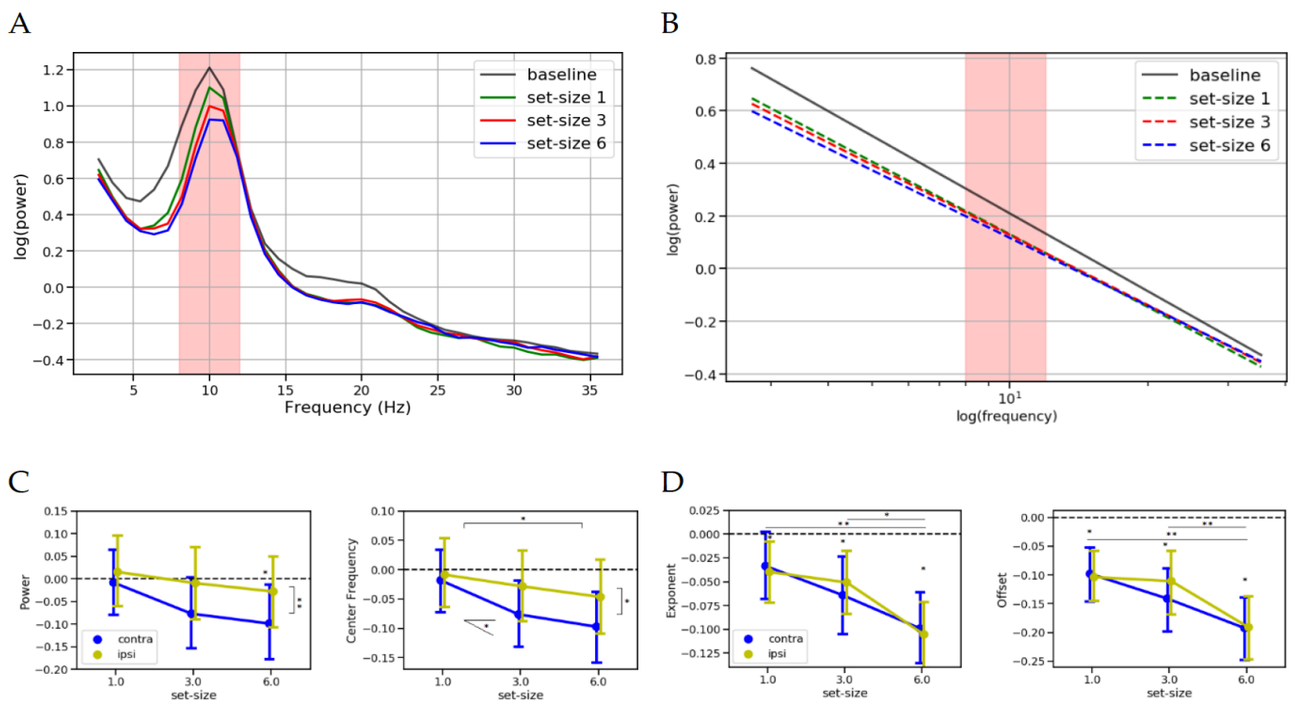


Figure 5: Experiment 1 – alpha range: Set-size has a strong effect on the aperiodic signal, and a moderate effect on the periodic components. A) Shows the power spectrum of occipital electrodes for the baseline period and the three set-sizes. B) Shows the same, but for the aperiodic signal. Highlighted in red is the alpha frequency range (8 – 12 Hz). The set-sizes are collapsed over ipsi- and contralateral and the baseline shown was averaged over all conditions. C) The corresponding values for the periodic components, relative alpha power (left) and center frequency (right). D) The corresponding values for the aperiodic components, exponent (left) and offset (right). Blue lines represent the contralateral side and yellow lines the ipsilateral side. *$p < 0.05$; **$p < 0.001$. Errorbars represent the 95% confidence interval.

(Figure 8C&D). However, the aperiodic offset was significantly reduced during memory maintenance, but only for poor performance (W = 36, p = 0.004, d = -0.688).

power between performance, as well as a difference between relative alpha power on hemispheres. Trials in which a participant performed poorly had more alpha power than on good performance trials. Furthermore, similar to experiment 1 but with a new set

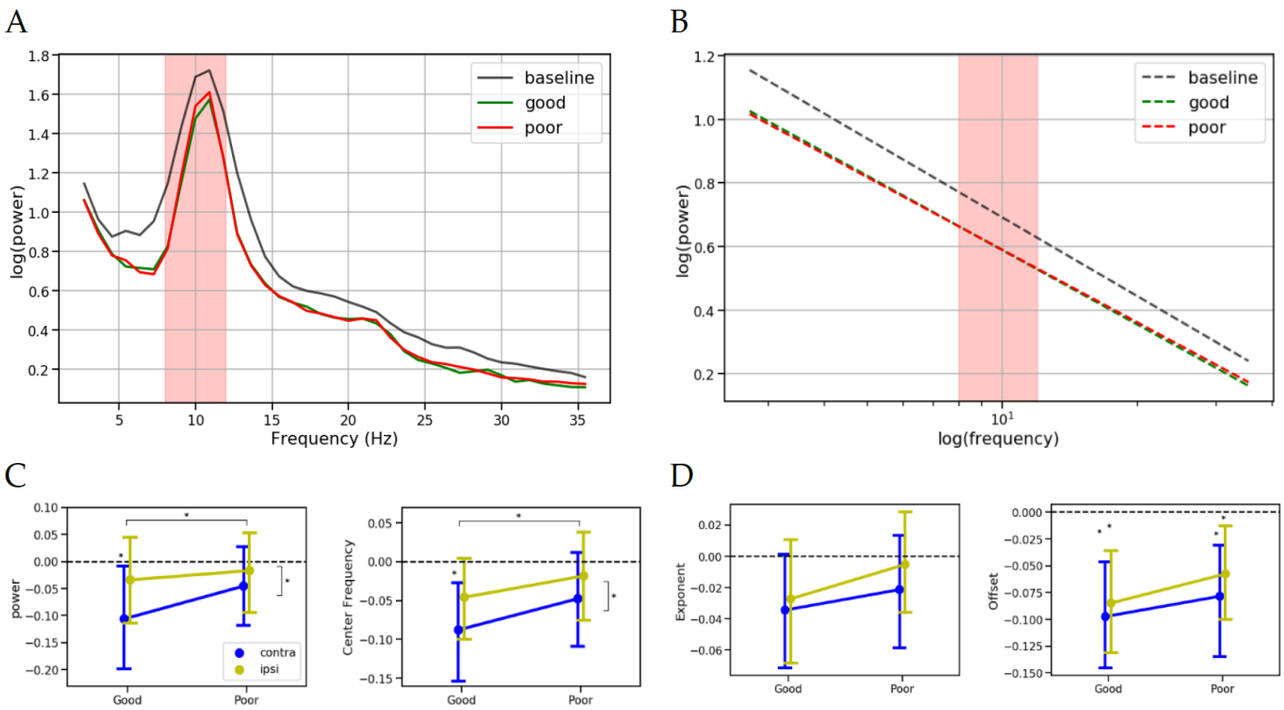


Figure 6: Experiment 2 – alpha range: Performance has an effect on the periodic components of alpha power, but not on the aperiodic signal. A) Shows the power spectrum of occipital electrodes for the baseline period, good and poor performance. B) Shows the same, but for the aperiodic signal. Highlighted in red is the alpha frequency range (8 – 12 Hz). The performances are collapsed over ipsi- and contralateral and the baseline shown was averaged over all conditions. C) The corresponding values for the periodic components, relative alpha power (left) and center frequency (right). D) The corresponding values for the aperiodic components, exponent (left) and offset (right). Blue lines represent the contralateral side and yellow lines the ipsilateral side. * p < 0.05. Errorbars represent the 95% confidence interval.

4 - Discussion

4.1 Summary of results

The goal of this research was to investigate the properties of lateralized occipital alpha power and midline frontal theta power, separating the relative oscillatory activity from the aperiodic signal. I sought to compare the results using this approach against canonical analyses, in which the absolute power is calculated from a narrow frequency band. First, I found that the contralateral hemisphere exhibits less relative alpha power than the ipsilateral hemisphere, relative to the attended side of the screen. In contrast to the original results (Adam et al., 2018), I could not statistically reproduce the results from experiment 1. Similarly, I did not find a decrease in relative alpha power with increasing set-size. In addition, I expected to see an interaction effect between hemisphere and set-size, since that was the main finding of the original paper, however, this was not the case for relative alpha power with the newer approach, nor when I replicated their approach. Again, the trends are visually similar and as expected, but lack statistical reliability.

Second, when separating the data into good versus poor performance in experiment 2, there is a difference in relative alpha

of participants, it is clear again that the contralateral side has suppressed alpha power, compared to the ipsilateral side. However, no interaction effect was found for lateralized relative alpha power on performance. This is not so surprising, since it corresponds to the replicated results based on absolute lateralized alpha power, and the original results, in which there was so interaction effect between performance and hemisphere.

Third, I was able to replicate the results for theta power using a time-frequency analysis. However, when separating oscillatory activity from the aperiodic signal, it turned out that relative theta power was not statistically different between good and poor performance. This applies to the group that exhibited theta power and the group that did not. What is different between these group is the aperiodic offset. The group exhibiting theta power had a reduction in offset for both good and poor performance. Whereas the other group only shows a reduction in offset for poor performance, but not good performance. Thus, I suggest a new interpretation of the data: a decrease of absolute theta power should be interpreted as a decrease in the aperiodic signal and not in oscillatory activity.

Taken together, I conclude that separating the aperiodic signal from oscillatory power is more informative than extracting the

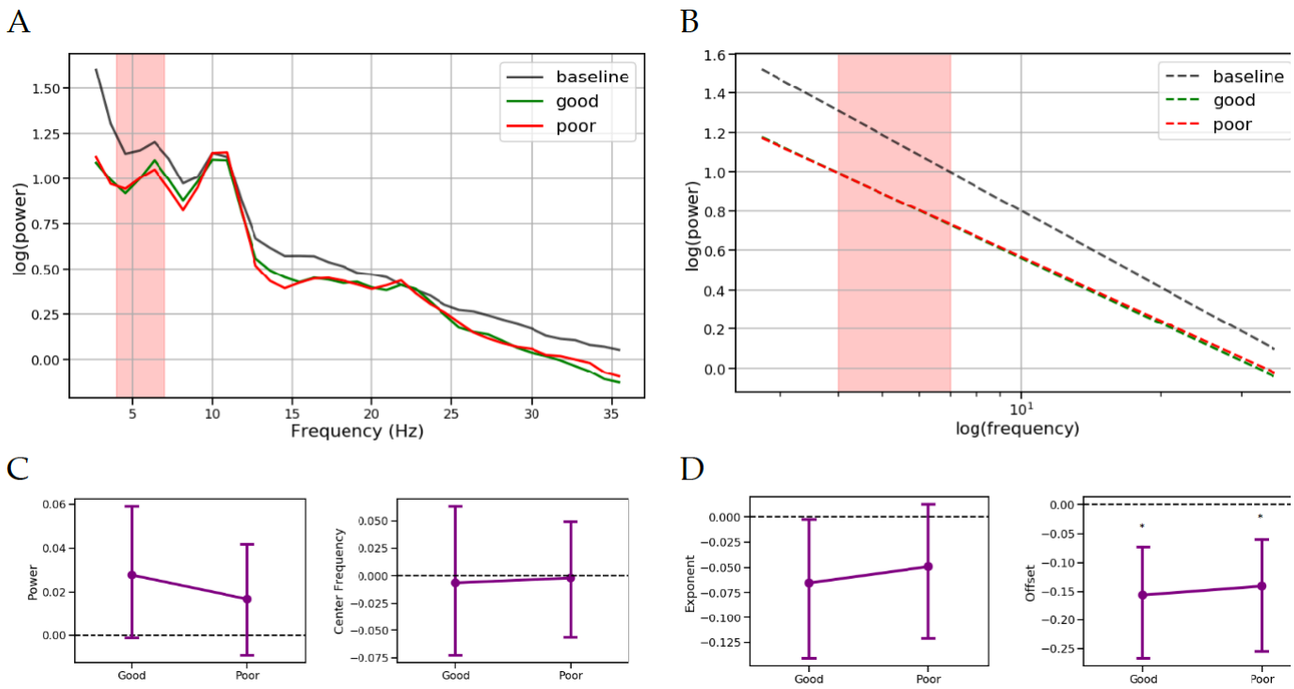


Figure 7: Experiment 2 – theta range – theta group: Aperiodic offset drops during memory maintenance for participants that exhibit relative theta power. A) Shows the power spectrum of occipital electrodes for the baseline period, good and poor performance. B) Shows the same, but for the aperiodic signal. Highlighted in red is the theta frequency range (4 – 7 Hz). The baseline shown was averaged over both conditions. C) The corresponding values of the periodic components, relative theta power (left) and center frequency (right). D) the corresponding values for the aperiodic components, exponent (left) and offset (right). * $p < 0.05$. Errorbars represent the 95% confidence interval.

absolute power from a narrow frequency band. By doing this, you exclude other possible reasons that could not have been determined when extracting the absolute power with narrow band analysis: 1) the peak shifts out of the canonical frequency range, 2) there is a shift in offset or, 3) a shift in exponent (Haller et al., 2018).

4.2 Interpreting the aperiodic signal

Even though there is extensive literature into midline frontal theta power, I discovered that half of the participants do not exhibit oscillatory theta power. This means that perhaps most of this research filters the aperiodic signal, without an oscillation being present in the data (Figure 7&8). One could expect a difference in the aperiodic exponent being the true driving force of observed differences in theta "power", as has been shown in aging in particular (Dave et al., 2018; Voytek et al., 2015). However, the group without theta power does not show a difference in the exponent between good and poor performance, nor does the group with theta power. One possible explanation for this could be that the exponent is an inherent property within participants, and less task-specific.

Instead, it seems that the aperiodic offset can explain the results better than the exponent. At least for these results, there is a general decrease in offset, but not exponent during the task, compared to baseline. When looking at the aperiodic offset in the group without theta power, there is no difference between good and poor performance. Nevertheless, poor performance is characterized by a significant drop in the offset compared to baseline, an effect that is not significant for good performance. Overall, whether this decrease is dependent on performance is ambiguous and needs further investigation.

Moreover, this literature suggests that good performance is correlated to a tonic decrease (Adam et al., 2015, 2018; Bender et al., 2019; Brzezicka et al., 2015; Jensen & Tesche, 2002), and a phasic increase (Klimesch, 1999) in theta power. This is true, according to the time-frequency analysis (Figure 4C&4F). However, it seems that this has nothing to do with oscillatory theta power, but instead is due to a shift in the aperiodic offset (Figure 7B&8B). Perhaps a change in total theta power consists of a change in relative power and a shift in the aperiodic signal in the same direction. Total theta power might be significantly different between good and poor performance. But independently, the aperiodic signal and relative theta power are not significantly different between good and poor performance. Both components could move in the same direction and add up to a significant change in total power.

What happens during the short phasic increase in theta power during the presentation of the memory array is up for speculation. It is too short of a time period to generate a reliable power spectrum and is therefore outside of the scope of analyzing the aperiodic signal. However, since it is shortly after the memory array onset and the cue onset, it is probably caused by ERPs.

Surprisingly, I was unable to statistically replicate the results from experiment 1. The original paper (Adam et al., 2018) finds an interaction effect between set-size and hemisphere, which indicates that contralateral alpha power is more suppressed for higher set-sizes than lower set-sizes. The main effect of set-size on total alpha power was replicated, but this was endependent of hemisphere. Nevertheless, the trend was replicated (Figure 4A&E). Besides, the outcome of relative alpha power was not statistically reliable, but the trend is; relative alpha power is higher

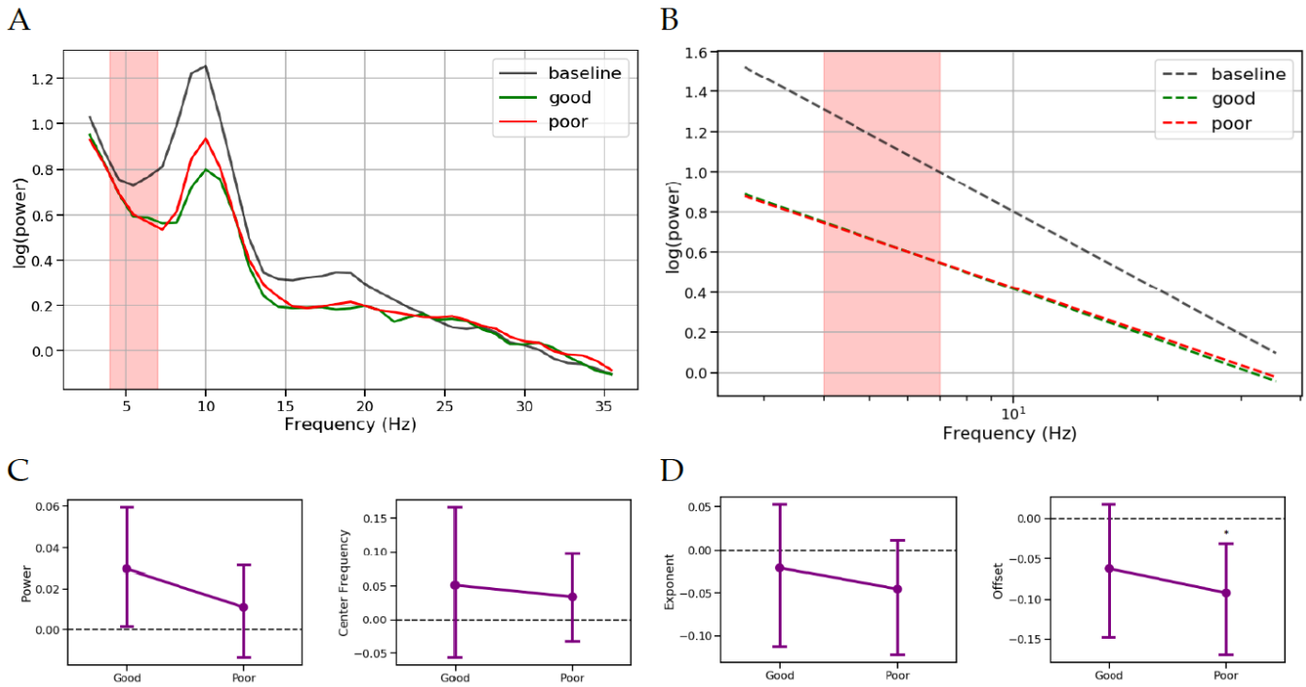


Figure 8: Experiment 2 – theta range – no-theta group: Aperiodic offset drops during memory maintenance for poor performance for participants that do not exhibit relative theta power. A) Shows the power spectrum of occipital electrodes for the baseline period, good and poor performance. B) Shows the same for the aperiodic signal. Highlighted in red is the theta frequency range (4 – 7 Hz). The baseline shown was averaged over both conditions. C) The corresponding values of the periodic components, relative theta power (left) and center frequency (right) D) The corresponding values for the aperiodic components, exponent (left) and offset (right). * p < 0.05. Errorbars represent the 95% confidence interval.

for lower set-sizes than higher set-sizes, but no interaction effect was found. The difference between these findings and the original results were unforeseen. Perhaps what could cause it is that I used a trial-by-trial baseline for both analyses, whereas the original paper applies the baseline on the average per condition and per subject. Or, it could be an effect of separating the relative power from the aperiodic signal. Set-size could have a more drastic effect on absolute power when both components of the signal change in a similar direction, an effect that is insignificant when analyzed individually.

Nevertheless, these results show that changes in the aperiodic signal are task-related, but not dependent on performance. It is also in line with previous research showing that the aperiodic signal contains valuable information. It is linked to the E:I balance in the brain (Gao et al., 2017; Lombardi et al., 2017), and it better describes aging (Dave et al., 2018; Voytek et al., 2015; Waschke et al., 2017) and neurological disorders (Leemburg et al., 2018; Peterson et al., 2017) than band power, or band ratios do alone.

4.3 Evaluation of single trial power spectra

The averaged power spectra look quite different than some of the results from the individual trials. This is for instance the case for the center frequency of the alpha peaks and the aperiodic differences seen in experiment 1. These are statistically different per condition, even though they seem similar in the power spectrum (Figure 5 A&B). One explanation is that the output from FOOOF is less reliable at the level of single trials due to high noise in the power spectra across short times windows (see supplementary material). Furthermore, the goodness of fit was similar between conditions, indicating that this cannot explain the data. Only 1100 ms were used for the retention period, which comes down to 275 time points with a sampling frequency of 250 Hz. The length of the window for the Fourier transform was the same length as the number of data points. This is why the power spectra are noisy: the window cannot slide over the signal to smooth it. However, this single-trial approach was necessary to baseline per trial, which is an important property that is lost when the power spectrum is averaged before applying the model. Lastly, even when analyzing the whole trial and creating a smoother power spectrum, the model fit was still not perfect. It missed some participants peaks in the theta range, due to a large adjacent peak in the alpha range. Or it would incorrectly fit two peaks instead of one wider peak in the alpha range, creating the illusion of a theta peak that was not present because the alpha peak bleeds into the theta range (Figure 8A). To address this issue, we manually selected participants with midline frontal theta power using visual analysis. Of course, this problem is not isolated to this analysis, since narrow band filters will also include unwanted alpha power in these participants. Therefore, part of the results for theta power from the original study can perhaps be explained by including unwanted alpha power on accident.

4.4 Future research

The next step for this dataset in particular is to investigate the relation between midline frontal theta and occipital alpha power within participants. In this analysis, the groups were separated based on exhibiting midline frontal theta power or occipital alpha power independently. But it would be interesting to see whether

participants that exhibit strong occipital alpha power, also have "frontal" alpha power measured on the midline frontal electrodes and if this interferes with theta activity. Another step is to see whether theta power is correlated to overall task performance. A similar analysis could be applied to alpha power measured on midline frontal electrodes.

Lastly, the theta frequency range varies widely in the literature. Some papers use 4 to 7 Hz (Adam et al., 2015, 2018), while other use 3 to 6 Hz (Brzezicka et al., 2015). Moreover, another method is to first look at a power spectrum, either grand average or per participant, and then define the frequency range of interest on the presence of oscillatory peaks. Doing so could then lead to theta power being described in the range of 7 to 8,5 Hz (Jensen & Tesche, 2002). For the data used in this experiment, it was particularly important to distinguish theta power from alpha power, which has to be done per participant by detecting peaks in their power spectrum. Interestingly, when reanalyzing the data used in this research with a frequency range of 4 to 8 Hz, instead of 4 to 7 Hz, the results are quite different (see supplementary material). Relative theta power is higher for good performance than poor performance when defining the theta range up to 8 Hz. Thus, it is interesting to see if the results will be different after excluding the possible interference of alpha power and then determining the theta frequency range per participant, instead of choosing this beforehand.

4.5 Take home message

In summary, researchers should refrain from methodological monism (Roberts et al., 2015), and include the aperiodic signal into their electrophysiological analysis. Because, as I have shown, including the aperiodic signal is vital to determine whether oscillatory activity is actually present in a certain frequency band. Besides, changes in the aperiodic signal can also be related to behavior. In this case, considering the contributions of the aperiodic signal in analysis led to a re-interpretation of the mechanism of midline frontal theta power.

Notes

About the artists

Artwork: Front Cover Illustration

Artist: Mengli Feng

Description: The work was aimed at expressing the idea of “the art of neuroscience” by colours. I guess there is a side of science that is fun and colourful and full of imaginations.

Artwork: Back Cover Illustration

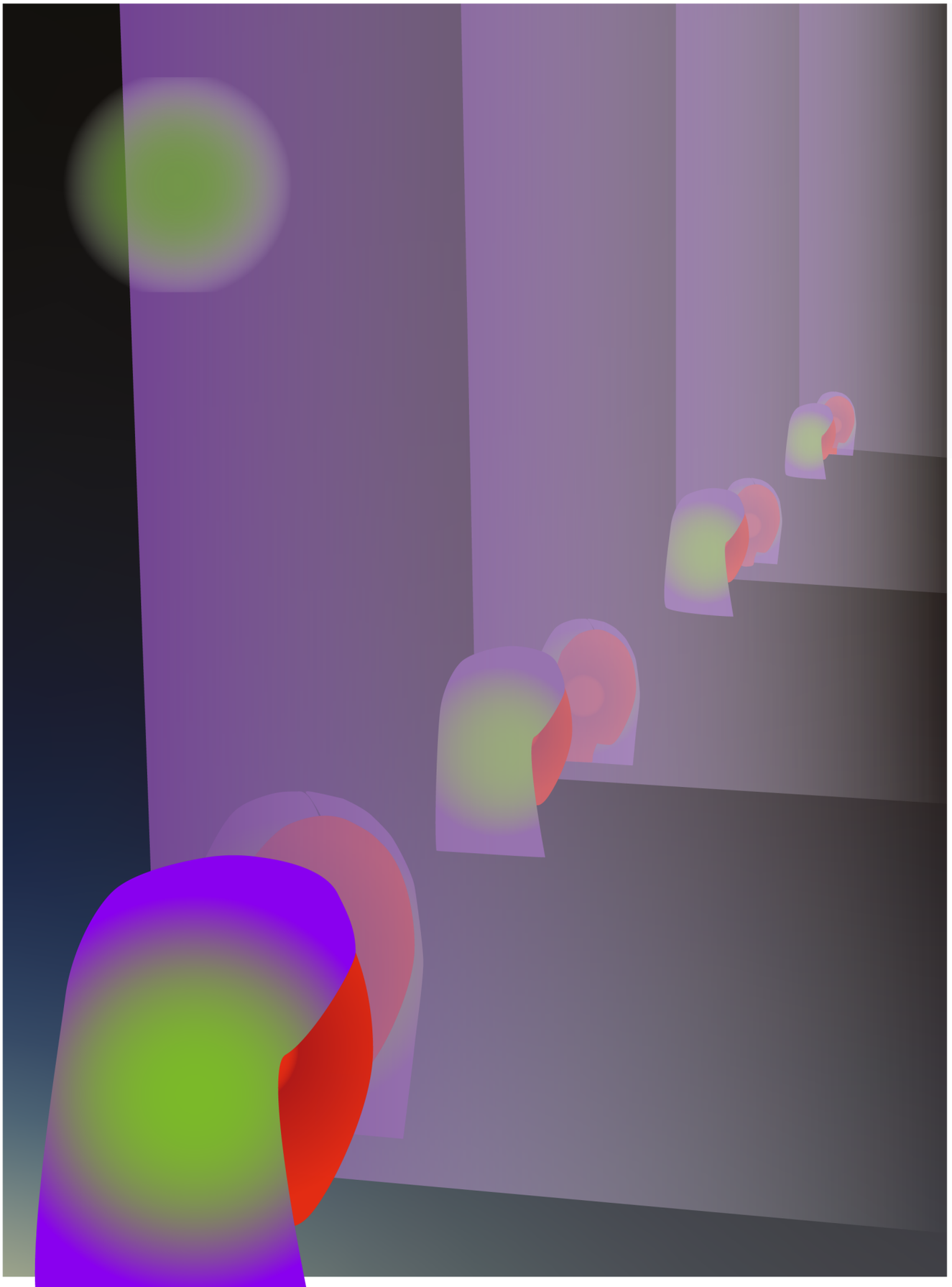
Artist: Michelle Kühn

Description: Inspired by the idea to depict introspection, this artwork portrays the process of thinking about thinking, in a slightly less abstract way than the poster design overleaf.

Artwork: Poster Design (overleaf)

Artist: Daan Kuik

Description: The idea for this work was to represent the act of introspection in a more abstract manner. I wanted to leave out all references to the brain and neurons; instead using a magnifying glass aimed at a mirror to represent the act of looking at oneself.



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