Is there is a burden attached to synaesthesia? Health screening of synaesthetes in the general population

ABSTRACT

Synaesthesia has long been considered a benign alternative form of perception most often associated with positive rather than negative outcomes. The condition has been associated with a variety of cognitive and perceptual advantages, including benefits in memory, processing speed and creativity. It is not currently recognised in the DSM-IV. Recently however, several studies have raised the question of a possible link between synaesthesia and clinical conditions. Here, we present the first large-scale screening of the general population in which we (a) objectively identified grapheme-colour synaesthetes and (b) elicited information from our participants about a range of clinical conditions. We compared the prevalence rates of these conditions in synaesthetes versus non-synaesthetes to establish whether any conditions were found at a higher rate among synaesthetes. In our initial study screening 3742 people (95 synaesthetes and 3647 controls) we found initially that grapheme-colour was significantly comorbid with two conditions (anxiety disorder and obsessive compulsive disorder). In our second study, screening a new population of 120 synaesthetes and 166 non-synaesthetes, we replicated our finding that grapheme-colour synaesthesia is comorbid with anxiety disorder. At the same time we also addressed a methodological concern that likely elevated rates of OCD in Study 1. We consider the aetiology of synaesthesia to determine whether there may be a shared genetic or neurological basis with anxiety disorder, and we question the status of synaesthesia within a mental health framework.

Key words: Synaesthesia, comorbidity, anxiety, OCD, health

INTRODUCTION

Synaesthesia is a condition in which every-day stimuli trigger unusual secondary associations. For example, hearing sounds might be accompanied by the perception of colours in the visual field (Ward, Huckstep, & Tsakanikos, 2006), or reading words might cause sensations of flavour (Simner & Ward, 2006). Synaesthesia is a multi-variant condition with a wide range of possible triggers (music, reading, eating etc.) and possible synaesthetic outcomes (sensations of colour, taste etc.). One well-studied variant is *grapheme-colour synaesthesia* in which letters or digits give rise to impressions of colour (e.g., A might be deep red; 7 might be light turquoise). These colours are seen either projected into space (e.g., overlaid on the written type-face during reading) or as strong mental imagery in the mind's eye (Ramachandran & Hubbard, 2001). Grapheme-colour synaesthesia affects approximately 1-2% of the population (Carmichael, Down, Shillcock, Eagleman, & Simner, 2015; Simner et al., 2006) and is the focus of the current study in which we investigate whether synaesthesia shows comorbidities with a range of clinical health conditions.

Synaesthesia has been associated with a variety of cognitive and perceptual advantages, including benefits in memory (Rothen, Meier, & Ward, 2012), processing speed (Simner & Bain, 2017), visual search (Ramachandran & Hubbard, 2001), creativity (Ward, Thompson-Lake, Ely, & Kaminski, 2008) and empathy (Banissy & Ward, 2007). The condition is therefore generally considered to be a benign atypical variant of perception, most often associated with positive rather than negative outcomes. Although the traditional portrayal of synaesthesia in the scientific literature reflects this view, a small body of research is emerging suggesting synaesthesia may also be associated with a set of clinical outcomes. However, some of the evidence in this emerging field comes from case studies of individual synaesthetes (Armel & Ramachandran, 1999; Jacome, 1999) who also happen to have other conditions (e.g., temporal lobe epilepsy and retinitis pigmentosa respectively). This case-study approach makes it difficult to draw conclusions about whether these

conditions might be causally linked or whether they co-occurred simply by chance. Recently a small number of group studies have shown significantly elevated rates of verified synaesthesia in two patient populations. Carruthers, Miller, Tarrier, & Whorwell (2012) screened a group of 200 patients with irritable bowel syndrome (IBS; e.g., Azpiroz et al., 2007) a visceral hypersensitivity in which patients also happen to show sensitivity to external stimuli (e.g., sound). Carruthers and colleagues found approximately three times the expected rate of synaesthesia in IBS patients compared with a non-clinical control sample. Similarly, Neufeld et al. (2013); see also (Baron-Cohen et al., 2013) found higher rates of synaesthesia in a sample of 29 patients with Asperger syndrome, a type of autism spectrum condition (ASC). Although their sample was small, Neufeld et al. found that the rate of synaesthesia was almost nine times higher in ASC participants (17.2%) than might otherwise be expected in the general population (using a value of 2.0%, taken from Simner et al., 2006).

In these studies, patient groups were screened for synaesthesia using an objective diagnostic test. With less formal screening (self-declared), Jonas and Hibbard (2015) questioned 253 female participants about both synaesthesia and migraine and found that certain types of synaesthetic triggers (scents, tastes, emotions, personalities, and visual triggers) were associated with higher rates of headache-with-visual-disturbances. They also found that variants of synaesthesia triggering tactile sensations were associated with migraine-with-aura. Jürgens, Schulte, & May (2014) have also suggested that migraines-with-auras might come with transient synaesthesia as a symptom. However, in the studies of migraine, synaesthesia was not objectively verified throughout the samples. Importantly self-declared data are known for its limitations (see Simner et al., 2006). Furthermore, Rich, Bradshaw, & Mattingley (2005) found that self-reported migraine was no more common in 192 synaesthetes, 70% of which were independently verified by an

objective diagnostic test (although Rich et al. did not distinguish between migraines with and without auras, nor did look within different types of synaesthesia).

As well as elevated synaesthesia within patient groups, there may also be evidence of elevated pathology within synaesthete groups. Simner, Carmichael, Hubbard, Morris and Lawrie (2015) suggested a possible link between synaesthesia and the radiological profile associated with multiple sclerosis (MS). Simner et al. observed significantly elevated rates of MS or radiologically isolated syndrome (RIS, the neurological profile of MS in the absence of clinical symptoms) in groups of synaesthetes self-referring for neuroimaging research studies. However, participant numbers were very small in that study, hence caution should be exercised in interpretation of those results. In summary, it is possible that synaesthesia might significantly co-occur with at least four different types of clinical conditions, although the small sample sizes in these previous studies (especially Simner et al., 2015) and the lack of independent verification of synaesthesia in some studies mean their results should be viewed with caution.

The studies reviewed above show it is possible to tackle the question of comorbidity by examining the prevalence of synaesthesia in a group of patients with a particular condition (Baron-Cohen et al., 2013; Carruthers et al., 2012; Neufeld et al., 2013b), or indeed by examining the prevalence of a particular condition within a group of synaesthetes (Simner et al., 2015). A third approach is to conduct a large-scale population study in which the sample is assessed both for synaesthesia and a range of health conditions at the same time, and this is the approach we take here. In Study 1 we screened approximately 4000 members of the general population, giving each subject not only a diagnostic test for grapheme-colour synaesthesia, but also a comprehensive health questionnaire in which they could report a range of 24 different diagnosed health conditions. Using this approach we were able to divide our sample into synaesthetes and non-synaesthetes and compare the rates of the particular conditions across the two groups, and in comparison with the rates from published

population-wide norms. In Study 2 we addressed a possible methodological issue that arose from Study 1 and we successfully replicate a subset of our initial findings with a revised methodology. In summary, across two studies we test the hypothesis that synaesthesia may be comorbid with one or more clinical conditions.

STUDY 1

METHODS

Participants

Three thousand eight hundred and ninety three participants took part in our study (55% female, 45% male; mean age 28.3, range 16.0-92.7, *S.D.* 14.3). Participants were recruited in three waves between January 2013 and September 2014 as part of a large-scale, centrally co-ordinated research project. Collection of data at three time points (henceforth "waves") was necessary as a large sample was required for statistical power due to the low prevalence of Grapheme-Colour synaesthesia and some health conditions. This project enlisted approximately 470 student RAs, each opportunistically recruiting 8 adult participants, aiming for half to be female (see Carmichael et al., 2015; Simner & Carmichael, 2015 for full details). RAs used uniform scripted instructions, and aimed to reduce self-referral biases. Specifically, RAs pre-selected a small cohort of potential participants and sent targeted invitation letters to these individuals while not disclosing the topic of synaesthesia. (In contrast, RAs did not post an advert to a large group of people inviting anyone to "take part in a synaesthesia study" – which would likely increase the proportion of synaesthetes in our testing population.)

All subjects were screened for grapheme-colour synaesthesia. On the basis of this screening, our sample was subsequently divided into 95 synaesthetes (58% female; mean age 21.7, range 16.4-70.8, *S.D.* 7.0) and 3647 non-synaesthetes (55% female; mean age 28.7, range 16.0-90.5, *S.D.* 14.4). An additional 199 participants were excluded from our study. Twenty-nine of these

encountered an equipment failure; 48 participants gave an obviously false date of birth (e.g., 2013), and the remaining 122 were removed because their status was ambiguous: they completed our study and self-reported synaesthesia but did not pass our objective diagnostic test for synaesthesia. (i.e., These 122 participants conflicted in self-report vs. objective testing, and so had an ambiguous status in this regard). Our study was approved by the University's Psychology Research Ethics Committee, and the task took approximately 20 minutes on average.

Materials and Procedure

Participants completed a two-part online test in which they first filled out a health questionnaire, and then took a screening test for grapheme-colour synaesthesia. Participants completed the study at home, via a URL, and began by first providing consent and demographic information including date of birth, handedness and sex. The following two tests were then completed in turn.

Health questionnaire. Participants were presented with a self-report questionnaire in which they saw 24 health conditions on-screen, and were asked the following question: "*Have you ever been diagnosed with any of the following conditions? Please click all the boxes that apply to you.*" These 24 conditions were given in single randomised order and were as follows: anorexia, anxiety disorder, attention deficit (hyperactivity) disorder (ADD/ADHD), bulimia, depression, obsessive compulsive disorder (OCD), schizophrenia, autism, Asperger syndrome, dyslexia, allergies, asthma, coeliac disease, chronic fatigue syndrome 'M.E.', Crohn's disease, eczema, epilepsy, hay fever, insomnia, IBS, migraine, multiple sclerosis (MS), sleep apnoea, and stomach ulcers. A check box was provided next to each condition, so participants could click anywhere between zero and twenty-four different boxes. This yes/no measure allowed point estimates of prevalence to be collected for each condition for all participants, before they were asked any information regarding synaesthesia. We split autism spectrum conditions (ASCs) into "autism" and "Asperger syndrome", although these conditions were combined in our analyses. The 24 conditions were

selected to represent a broad range of clinical disorders present in the population, including IBS, MS, ASC and migraine that have been questioned alongside synaesthesia previously.

Synaesthesia assessment. On completing the health questionnaire, participants advanced to the synaesthesia assessment. There are many different types of synaesthesia but we screened for grapheme-colour synaesthesia in particular because it is a well-understood and widely researched variant of the condition, and it can be diagnosed with a short effective screening test. In our screening, we used the widely accepted test for grapheme-colour synaesthesia taken from the *Synesthesia Battery* on-line interface (Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007) which we cloned with permission from the authors (see Carmichael et al., 2015) for details of our cloning). This test had two components. First, participants were presented with a question to allow them to self-report whether they believed they had synaesthesia. The question used has been well validated and asks "*Do numbers or letters cause you to have a colour experience?*". Participants responded with a separate checkbox for letters and for digits. If participants indicated that they saw neither letters nor digits in colour, they advanced to an exit page thanking them for their participation, and they were categorised as non-synaesthetes (following the widely used diagnostic test). Those who respond in the affirmative were given an objective test for grapheme colour synaesthesia, described below.

In the objective test for synaesthesia, participants individually viewed the letters A-Z and/or the digits 0–9 (according to what they had described as triggering their synaesthesia). Each grapheme was shown three times in a fully randomised order. On each trial, participants indicated their synaesthetic colour for the displayed grapheme by selecting the colour from an on-screen palette of 16,777,216 colours. Their colour-choices were then compared across the three selections for each grapheme (e.g., we compared the three colours a subject selected for the letter A) to establish how far away in colour space those three chosen colours were. Standard RGB colour space was

used, along with city block distance to measure consistency. Participants were also allowed to click a 'no colour' button, if they had no synaesthetic colour associations for any of the graphemes presented. Following the standard protocol, this distance was then averaged across all graphemes and normalised to produce one score as the test output. A small score reflects consistent colours (i.e., selections for the same grapheme were close in colour-space); and a score less than 1.43 considered to be a reliable threshold for distinguishing between synaesthetes and non-synaesthetes when using the RGB colour space with city block distance (see Carmichael et al., 2015; Rothen, Seth, Witzel, & Ward, 2013).

RESULTS

Validating our methodology. In our study we are seeking to determine the rates of clinical conditions across our two different subject groups (synaesthetes and non-synaesthetes) by asking participants to self-report their health diagnoses. Before analysing our data, we first independently validated our methodology by comparing our self-declared rates with the known prevalence of each health condition in the general population. Figure 1 below shows the self-reported rates of diagnosis of each health condition in our own sample (in dark grey, combining synaesthetes and non-synaesthetes) and the published rates available from the medical literature (in light grey). Population-wide estimates of prevalence were in line with our sample prevalences (see supplementary material for full details).

Figure 1 insert here

Clinical rates in synaesthetes versus non-synaesthetes. We next considered the rates of each clinical condition across our participant groups (our synaesthetes and non-synaesthetes) to determine whether any conditions were found at significantly differently rates in synaesthetes. Before comparing participant groups we inspected their demographic makeup to determine whether any other group differences were present in age, sex, etc., which might independently

determine overall health. Our synaesthete and non-synaesthete samples were evenly matched on sex (57.9% and 54.6% female respectively) and handedness (87.4% and 89.3% right-handed respectively). However, there was a significant age difference between synaesthetes (mean 21.7 years, *S.D.* 7.0) and non-synaesthetes' (28.7 years, *S.D.* 14.4), $t(115.9) = 9.183$, $p < .001$. Thus, our models below include age as a variable where relevant. Two tailed tests of significance were used for all analyses ($p < .05$), but results meeting one tailed significance thresholds ($p < .10$) were considered as trending associations and explored further (see below).

To limit repeated comparisons and avoid over-fitting, we first made *a priori* predictions about which of the 23 conditions to include in our binary logistic model and our principle was based on two considerations. First, we *a priori* excluded those conditions that were prevalent at less than 1% in the general population, because they would have to be hugely more common in synaesthetes (greater than 5 times more common) for our sample size to allow us to detect any significant effects[1]. By this measure we excluded eight conditions: anorexia, bulimia, coeliac disease, chronic fatigue syndrome (ME), Crohn's disease, epilepsy, MS, and schizophrenia (see supplementary material). The remaining 15 conditions were therefore candidates for our model. To avoid over-fitting we next conducted individual binary logistic regressions for each condition to assess individually whether synaesthesia predicted each condition, regressing out age where appropriate This removed a further 11 conditions (ADD/ADHD, asthma, depression, dyslexia, eczema, hay fever, insomnia, IBS, migraine, sleep apnoea, stomach ulcers) which showed no significant relationship with synaesthesia, even at uncorrected *p* values (see supplementary material for full details).

[1] We were aware of this issue when designing our study but chose to include the low prevalent conditions within our methods in the expectation that future repetitions of our protocol might eventually allow sufficient sample size to revisit these conditions in future analyses.

There were four remaining conditions that showed significant relationships with synaesthesia at an uncorrected level (allergies, OR[2] = 1.6, p = .034; anxiety disorder, OR = 2.7, p = .002; ASC, OR= 4.9, p = .04; and OCD, OR= 6.1, p < .001). To address the issue of multiple comparisons we entered into our model only those conditions that survived correcting for 15 comparisons, and/or showed evidence of replicability across waves in our study. First, then, there were two conditions surviving at the stringent corrected alpha of p = .0033 (anxiety disorder and OCD). We next inspected the final two conditions that did not survive this rigorous correcting (ASD, allergies) in order to evaluate whether there was independent evidence to assume their uncorrected significance had not been spurious. For this we inspected their performance within the individual waves of our study. These waves contained 34 synaesthetes, 1403 non-synaesthetes (wave 1), 36 synaesthetes, 1281 non-synaesthetes (wave 2), and 25 synaesthetes, 963 non-synaesthetes (wave 3). We repeated our analysis within each wave (i.e., a binary logistic regression predicting synaesthesia given the health condition while regressing out age where appropriate). Here we found evidence that an association (either significant or trending towards significance) was replicating across waves for ASC (Wave 1 OR = 8.5, p = .05; Wave 2 OR = 6.1, p = .099; wave 3 could not be modelled due to too few cases overall of ASC) but was not replicating across waves for allergies (Wave 1 OR = 1.2, p = .62; Wave 2 OR = 1.9, p = .07; Wave 3 OR = 1.9, p = .15). We therefore entered ASC into our model along with anxiety disorder and OCD but rejected allergies.

Hence we included three items in our final model. In our model we considered whether these three conditions linked to synaesthesia are themselves related. We performed a hierarchical binary logistic regression to model the likelihood of being a synaesthetes given age (treated as grand-mean centred and quadratic to model non non-linear effects) alongside: anxiety disorder, ASC,

[2] OR = Odds Ratio, the odds of being in the dependent group (e.g., having anxiety disorder) based on independent group membership (e.g., synaesthete); a score above 1 signifies a greater likelihood, and below 1 signifies a lower likelihood.

and OCD. Model 2 refined Model 1 by removing the least significant predictor with the highest *p* value. The outcome of these two models is shown in Table 1.

Table 1 insert here

As expected, age was a significant predictor of synaesthetic status in both models since older participants were significantly less likely to be identified as synaesthetes than younger participants (see Simner, Ipser, Smees, & Alvarez, 2017). In Model 1, OCD significantly predicted the likelihood of being identified as a synaesthete when age was controlled for, and anxiety disorder trended in that direction also (using a $p < .10$ threshold). The influence of ASC was non-significant and non-trending in this model (at $p = .10$). It should be noted that the binary logistic regression models shown here represent 'net' estimates, i.e., the estimate once other predictors have been taken into account. So, although synaesthetes were more likely to have had a diagnosis of Anxiety disorder and ASC independently on their own (reflected in an Odds Ratio of 2.7 and 4.9 respectively see Table 1), when other conditions are accounted for in Model 1 they are no longer significant at the conventional 5% level. This suggests that they may have been acting as a proxy for other predictors, or are partially subsumed by each other. After removing the least significant predictor (ASC), our Model 2 showed that OCD remained a significant predictor of synaesthesia and anxiety disorder trended towards significance (at $p = .06$). In this second model, the significant odds ratios were such that having OCD increased the likelihood of having synaesthesia 5.2 times over, whereas having anxiety disorder increased it by a factor of 1.9.

DISCUSSION

We investigated rates of clinical conditions in a large random sample of objectively-tested grapheme-colour synaesthetes, compared with non-synaesthete controls. Four conditions were found in significantly higher rates within synaesthetes, even when effects of age were factored out: allergies, anxiety disorder, ASC and OCD. After addressing the issue of multiple comparisons,

three associations remained (anxiety disorder, ASC and OCD) and were modelled together to look for co-dependencies. Our best fit model showed a significant effect of OCD in predicting synaesthesia and a near-significant effect (p = .06) of anxiety disorder.

STUDY 2

Our aim in Study 2 was to seek a replication for our findings while at the same time ruling out a possible sampling issue that could have affected our earlier results. This issue relates to how participants were classified as synaesthetes or non-synaesthetes in Study 1. We followed the scientific benchmark of using a 2-stage method: collecting self-reports, then verifying those who claim to have synaesthesia with an independent objective test. This method is the mostly widely used diagnostic test in synaesthesia research (see Simner, 2012 for a review of the multitudinous studies that use this method) and it rests on the asymmetry in synaesthesia-reporting: claims of synaesthesia are known to be unreliable and require verifying (see e.g., Simner et al., 2006) while claims of *not* having synaesthesia are assumed to be more accurate and so are taken at face value. Although we do not question this assumption here, we point out that this standard approach could cause unwanted effects in our own study. Specifically, non-synaesthetes simply had to answer one question while synaesthetes had to perform a long, repetitive, attention-demanding test. Finding that synaesthetes show higher traits of OCD in particular might therefore be because our test could perhaps select for this trait by causing a higher drop-out rate for less compulsive synaesthetes (i.e., compulsive synaesthetes would be more likely to persevere with a long, attention-demanding task). To address this, we conducted a second screening study in Study 2 on a new population of individuals, and this time gave the same test to both synaesthetes and non-synaesthetes. Once done, we again compared their health profiles, looking particularly at the four conditions flagged in Study 1 as significant in uncorrected tests: allergies, anxiety disorder, ASC and OCD. By adapting

the methodology in Study 2 so all participants completed both the health questionnaire and synaesthesia test, we removed the potential OCD confound.

A note of caution about power Grapheme-colour synaesthesia is a rare condition found in only 1-2.5% of the population (Simner et al., 2006; Carmichael et al., 2015). The hundreds of synaesthetes tested in our investigations were necessarily screened from thousands of subjects all individually screened (i.e., we screened approximately 40 times more than the number of synaesthetes finally recruited). Our article provides the largest sample of synaesthetes ever tested in this way but power analyses for Study 2 (specifying 80% chance of detecting with an alpha of .05) show that a challenging number of synaesthetes are required for sufficient power to replicate our findings on allergies (synaesthetes = 446; non-synaesthetes = 318), anxiety disorder (synaesthetes= 276; non-synaesthetes = 196), ASC (synaesthetes= 838; non-synaesthetes = 597) and OCD (synaesthetes = 140; non-synaesthetes = 99). Practical constraints necessarily limit the number of synaesthetes recruited, leaving our final sample size in Study 2 as synaesthetes = 112; non-synaesthetes = 157. Any failure to replicate findings from Study 1 may be due to power, and we address this in our study below with Bayes statistics.

METHODS

Participants

Three hundred and seventy-six participants took part in our study (90.4% female; 9.6% male; mean age 26.2, range 16-67 years, *S.D.* 8.3). An additional 19 subjects were tested but removed because they failed to follow task instructions (n=5; see *Methods*) or because their response to our question about gender placed them in a group that was too small to enter into our analyses (i.e., our gender question now included: ‘other’ n=4; ‘prefer not to say’ n=10). Our participants were recruited via a testing URL placed within a media article about synaesthesia written on the website of the news agency *Buzzfeed*. This news article described several types of synaesthesia and invited participants

to take part in our study by clicking an embedded URL testing link. As in Study 1, all subjects were screened for grapheme-colour synaesthesia, but now using the revised methods described below, which serve to remove a possible confound identified in Study 1 (see below).

Our sample was subsequently divided into grapheme-colour synaesthetes (n=112; 94.6% female; mean age 25.5, range 16-62, *S.D.* 7.4) and non-synaesthetes (n=157; 84.7% female; mean age 26.8, range 17-67, *S.D.* 9.0). One hundred and seven subjects were allocated to neither group and so were removed from the study, as before. These subjects completed our study and self-reported synaesthesia (like our synaesthetes) but did not pass our objective diagnostic test for synaesthesia (like our non-synaesthetes) or vice versa. In other words, they conflicted in self-report versus objective testing, so had an ambiguous status in this regard. Our study was approved by the University's Research Ethics Committee, and took approximately 20 minutes on average to complete.

Materials and Procedure

As in Study 1, participants completed a Health Questionnaire and an assessment for grapheme-colour synaesthesia. Our Health Questionnaire contained the four conditions identified in Study 1 as having shown significant relationships with synaesthesia at uncorrected levels, along with the question: "*Have you ever been diagnosed with any of the following conditions? Please click all the boxes that apply to you (you can click more than one…)*" The four conditions were phrased as: "*Allergies (including hay fever)*", "*Anxiety disorder*", "*Autism Spectrum Conditions (ASC or ASD): These include Autism, Asperger's Syndrome, Pervasive Developmental Disorder – Not otherwise Specified (PDD-NOS)*", and "*Obsessive compulsive disorder (OCD)*". In the event that our results might show a significant relationship with allergies, we included the option to specify the type of allergy (see supplementary material for full details). In the event that our results could show a significant relationship with ASC, we included the option to specify the type of ASC from

the following list: *Autism (but not recognised as Asperger's Syndrome)*, *Asperger's Syndrome*, *PDD-NOS,* or *I don't know*. These options were revealed to subjects only if they self-reported allergies or ASC respectively. Finally, we also included five dummy conditions which had not shown any significant link to synaesthesia in Study 1 (Insomnia, ADHD, IBS, migraine, and MS) to hide the focus of our study. This was to avoid a situation where a synaesthete might legitimately recognise a high proportion of conditions, and so be encouraged to malinger towards the remainder.

The synaesthesia assessment had the same two steps as in Study 1: in step 1 participants are asked whether they have synaesthesia and in step 2 they are given an objective (consistency) test for synaesthesia. The key difference to Study 1 was that all subjects completed step 2 (i.e., the objective consistency test for synaesthesia) irrespective of how they answered the self-report question in step 1. As before, participants who self-declared synaesthesia were given a consistency test for the trigger(s) they had specified (letters, numbers or both). Unlike before, participants who self-declared *not* having synaesthesia were randomly allocated a trigger-condition, and given the same instructions as synaesthetes. Both groups were told they would see a number or letter next to a colour palette and that they must pick 'the best colour' for each one. They were told they could choose any colour they like but should avoid choosing the same colour for everything (e.g., they should avoid choosing only red throughout; the five participants excluded from our cohort failed in this respect, see *Participants*). As before this test output the same consistency measure in the form of a colour-distance score calculated in the same way as in Study 1. The only difference in the interface between those who did and did not self-declare synaesthesia was that the former were given the option to specify 'no colour' for any given grapheme. This is because genuine synaesthetes can experience 'gaps' in their coloured alphabet, and so could express this using the

'no colour' button. The same button was not given to self-declared non-synaesthetes with the concern they could logically press it on every trial.

Finally there were several inconsequential differences between our presentation formats of Study 1 and 2 which arose from unrelated improvements made to our testing interface that were not tied to any hypotheses in the current study. For practical reasons, we now used our own in-house assessment for synaesthesia rather than a clone of the Synesthesia Battery. Our self-report question was now phrased as follows: "*Do numbers or letters have colour associations (ie. Which you've been aware of before now)? For example, do you tend to think the letter J is, say, purple? Or does the number 5 seem red, for example?"* Participants then selected a button to respond either "*Yes, I have this type of experience*", "*No, I do not have this type of experience*", "*No, not for numbers or letters but I have this for other things*". But just as before, participants who chose the first option were then given the opportunity to specify with a check box whether they had automatic colour associations from numbers or letters or both. Just as before, this was followed by the consistency test which presented each grapheme (A-Z, 0-9) three times in a random order and required participants to select a colour for each grapheme from an on-screen colour palette. This palette was equivalent across our studies in the number of colours, and in both studies subjects selected those colours from a vertical hue bar adjacent to a 'shade-box' which could modify the hue's saturation and luminance. In Study 2, the achromatic colours black/grey/white were at the edges of the shade box (which had saturation on one axis and luminance on the other) while in Study 1 these achromatic colours black/grey/white had been repeated on their own horizontal slider running from white to black underneath the shade box.

RESULTS

As in Study 1, grapheme-colour synaesthetes were those who self-declared synaesthesia and passed the objective consistency test for grapheme-colour synaesthesia with the required score of

<1.43 (see Study 1). Non-synaesthetes were those who self-declared *not* having synaesthesia (as in Study 1) but also produced a failing score (≥ 1.43) in the objective consistency test. Our synaesthete and non-synaesthete samples were evenly matched on age, $t(234) = 1.2$, $p = .2$, although there were significantly more females in the synaesthete group, $\chi^2 = 6.5$, df = 1, $p = .011$; see *Participants* for descriptive statistics). Thus, our model below predicting synaesthesia given different health conditions includes sex as a variable.

Clinical rates in synaesthetes versus non-synaesthetes. We tested four medical conditions, which had shown a significant relationship with synaesthesia at an uncorrected level in Study 1: allergies, anxiety disorder, ASC, and OCD. The rates of each condition in Study 2 were found to be higher in synaesthetes for Anxiety disorder (41.1% for synaesthetes vs 28.0% for non-synaesthetes) and ASC (2.7% for synaesthetes vs 0.6% for non-synaesthetes) but not for Allergies (35.7% for synaesthetes vs 41.4% for non-synaesthetes) or OCD (6.3% for synaesthetes vs 8.9% for non-synaesthetes). See supplementary material for full details.

We performed a binary logistic regression to model the likelihood of being a synaesthetes given sex and these four medical conditions, see Table 2. Sex was a significant predictor of synaesthetic status, as was anxiety disorder (showing independent effects), with no other effects significant.

Table 2 insert here

Given our concerns about power and sample sizes, we also conducted Bayes factors analyses. Bayes allows us to evaluate, for both significant and non-significant results, to what extent the data supports the hypothesis under investigation against the null hypothesis (Rouder, Speckman, Sun, Morey, & Iverson, 2009). A Bayes factor (*BF*) of < 0.33 provides strong support for the null hypothesis, a Bayes factor >3 provides support for the alternative hypothesis, and values in between indicate no firm conclusions should be drawn. Bayes factors were calculated from our regression model, using expected diagnosis rates taken from Study 1 and applying 1-tailed tests

for the three conditions we expect to replicate (ASC, anxiety disorder, allergies) and a 2-tailed test for OCD whose outcome might be methodology-dependent across our two studies. Our resultant Bayes factors indicate that no firm conclusions can be drawn from Study 2 about the rates of ASC (*BF* = 2.09) and OCD (*BF* = 0.96) in our data. However, there is strong support for the null hypothesis of no relationship between synaesthesia and allergies (*BF* = 0.27), and strong support for the alternative hypothesis that synaesthesia is predicted by anxiety disorder (*BF* = 9.6).

DISCUSSION

In Study 2 we tested whether grapheme-colour synaesthesia was associated with particular medical conditions while at the same time checking for a possible confound in Study 1, where synaesthetes and non-synaesthetes had been screened differently. In Study 2, we screened synaesthetes and non-synaesthetes with an identical test, and again asked them to self-report whether they had medical diagnoses for four conditions: allergies, anxiety disorder, ASC and OCD. We found that rates of anxiety disorder were higher in synaesthetes (41%) than non-synaesthetes (28%). In our model, the significant odds ratios were such that having anxiety disorder increased the likelihood of having synaesthesia two times over, and a subsequent Bayes analysis showed strong support for the association. No other condition was a significant predictor of synaesthesia, with Bayes analyses showing strong support for the null hypothesis for allergies (no link to synaesthesia) but that no firm conclusions could be drawn for ASC and OCD. However we point out that the numerical trend for OCD in Study 2 was in the opposite direction than found in Study 1.

GENERAL DISCUSSION

In two studies we investigated the rates of clinical conditions in samples of several hundred grapheme-colour synaesthetes, and several thousand non-synaesthete controls. Synaesthetes were identified by screening a large cohort of the general population, using an objective test that separated synaesthetes from non-synaesthetes, and rejected any individuals whose status was

unclear (e.g., those self-reporting synaesthesia but failing the objective test). We asked subjects to self-report whether they had been diagnosed with a range of medical conditions, and found across both studies that being diagnosed with anxiety disorder was a predictor of having synaesthesia. In Study 1 it was a significant predictor in isolation uncorrected at $p = .002$, and it survived correction to $p = .03$; it then remained in the combined model with OCD and ASC at $p = .06$. In Study 2, in an independent cohort with a novel testing methodology, it remained significant in our model at $p = .02$.

In addition to anxiety disorder, we also looked in detail at three other conditions, which we had also found in high rates within synaesthetes at uncorrected levels. These conditions were allergies, ASC, and OCD. After addressing the issue of multiple comparisons, three significant conditions remained in total (anxiety disorder, ASC and OCD) and were modelled together to look for co-dependencies in Study 1. Our best fit model initially suggested that having OCD was a predictor of synaesthesia although this study used a method that might artificially elevate rates of OCD in our sample of synaesthetes by screening them (but not non-synaesthetes) with a long, repetitive test. One symptom of OCD is a compulsive need to complete repetitive behaviours, and this in turn might mean synaesthetes with OCD were more likely to complete our repetitive test than synaesthetes without OCD. To remove this potential 'drop out' confound, we subsequently gave our test to both synaesthetes and non-synaesthetes in Study 2. We found that although anxiety disorder continued to be a significant predictor of synaesthesia in Study 2, OCD was no longer a significant predictor– and indeed was numerically trending in the opposite direction (higher OCD in controls). Bayes statistics suggested a lack of power in Study 2 for OCD and ASC, but firm evidence *against* a link to allergies, and firm evidence *for* a link to anxiety disorder. We note that our failure to find support for a link between synaesthesia and ASC belies the fact that such a link has been established in other studies testing more people with ASC (e.g., collected at autism clinics

(Neufeld et al., 2013b)). However, since we used random sampling methods we are necessarily modelling rare events (having synaesthesia) within a rare population (the 1% of people have autism; (Brugha T et al., 2012)) and this limits our ability to detect relationships even if they are present. We might also consider ASC within our broader set of results since previous studies suggest that over two-thirds of people with autism have been diagnosed with one or more additional psychiatric disorders, one of the most common of which is anxiety disorder (Simonoff et al., 2008). But since our sample size for ASC in particular was very small, and since we missed significance at any conventional level, we therefore give no further attention to this finding.

This is the first time the prevalence of a range of conditions has been tested in synaesthetes. We point out that while the increased prevalences reported here suggest an association between anxiety disorder and synaesthesia, it does not provide information regarding the origin or causality. We might therefore consider potential neurological and genetic commonalities with respect to synaesthesia and anxiety disorder below. Individuals who had been diagnosed with anxiety were almost twice as likely to be synaesthetes than non-synaesthetes in both replications. A review of previous literature suggests that a clue to this relationship may lie in the work of Banissy, Cassell, Fitzpatrick, Ward, Walsh and Muggleton (2012). Banissy and colleagues administered the Oxford-Liverpool Inventory of Feelings and Experiences (Mason & Claridge, 2006) to a group of 30 synaesthetes who experience synaesthetic colour, including grapheme-colour synaesthetes. Their findings showed synaesthetes had increased rates of disorganised and positive schizotypy, personality traits closely linked to decision making and social anxiety (but see Janik McErlean & Banissy, 2016). Until now it had been difficult to draw conclusions from their study because their recruitment method was self-referral rather than random sampling (and are likely to be personality markers tied to individuals who are willing to self-refer for psychological testing, above and beyond being a synaesthete per se). However, our own study appears to support their findings,

given that anxiety is a key aspect of positive/disorganised schizotypy (Debbané, Van der Linden, Gex-Fabry, & Eliez, 2009; Lewandowski et al., 2006) and since we found higher rates of anxiety disorder in a randomly-sampled group of grapheme-colour synaesthetes in Study 1. Like Banissy and colleagues (Banissy et al., 2012), we suggest therefore that the presence of synaesthesia may be an indicator of a broader phenotype, with synaesthetes exhibiting atypical profiles linked to higher rates of anxiety than non-synaesthetes.

Since our study revealed a significant comorbidity between grapheme-colour synaesthesia and anxiety disorder, we look to possible neural or genetic overlaps between the two conditions. Anxiety is a heterogeneous condition exhibiting a wide range of symptom dimensions (Terluin et al., 2014) including for example panic disorder, generalized anxiety disorder, specific phobias etc. This heterogeneity is reflected in the brain imaging literature on anxiety disorder, with different regions implicated in different underlying behaviours (Duval, Javanbakht, & Liberzon, 2015). Synaesthesia, too, shows heterogeneity both in its manifestations and underlying neurology. Different regions have been implicated even when scanning similar type of synaesthetes. Nonetheless, two regions in particular are worthy of closer attention. Altered white matter in terms of lower FA (fractional anisotropy) in the corpus callosum and the fasciculus (uncinate fasciculus, and superior longitudinal fasciculus (bilateral)) have been tied not only to anxiety disorder (McManus, Bebbington, Jenkins, & Brugha., 2016; Wang et al., 2016), but also to a number of types of synaesthesia (Simner et al., 2016) including the type of synaesthesia tested here (grapheme-colour) (Whitaker et al., 2014).

A similar heterogeneity presents itself in the genetics of anxiety disorder; a meta-analysis of GWAS studies of anxiety points to a condition in which a number of genes exert a small influence on a person's likelihood of developing anxiety disorders (Otowa et al., 2016). It is therefore a considerable challenge to use existing knowledge of anxiety genetics as a guide to identifying

regions of the genome which anxiety may share with synaesthesia. There are however, results from the anxiety literature that might merit closer examination in future studies. Domschke and Dannlowski (Domschke & Dannlowski, 2010) report an association between anxiety disorders and the serotonin polymorphism 5-HTTLPR, which codes for serotonin receptor 2A. Serotonin has been hypothesised to play a role in both developmental and acquired synaesthesia (Brang & Ramachandran, 2008; Brogaard, 2013; Luke & Terhune, 2013) although such accounts within synaesthesia have thus far been tentative. We present this discussion as highly speculative and point out that it would therefore be premature to draw definitive conclusions about shared genetic or neural architectures across conditions of anxiety and synaesthesia, but our study is the first step in showing an overlapping comorbidity in behaviour.

It should be noted that Study 2 attracted many more synaesthetes than was found in our randomly drawn sample (Study 1), given that recruitment in Study 2 was via a media article that would have particularly attracted synaesthetes. However, there is no reason to suggest that this recruitment bias would affect our conclusions. Nonetheless, the overall rates of anxiety disorder across the whole cohort were also notably higher in Study 2 (36.7%) compared to Study 1 (5.3%) and this allowed the relatively rare condition to be investigated with greater statistical power. This higher rate of anxiety disorder in Study 2 is likely to be, at least in part, because our latter sample were overwhelmingly female (90.4% female) compared to a balanced gender profile in Study 1. Anxiety disorder is found at significantly elevated rates in women (Kessler et al., 1994; Martín-Merino, Ruigómez, Wallander, Johansson, & García-Rodríguez, 2010; McLean, Asnaani, Litz, & Hofmann, 2011; McManus et al., 2016; Tyrer & Baldwin, 2006). Indeed, women are diagnosed more often than men for six out of the nine health conditions in Study 2 i.e., from our four target and five dummy conditions: anxiety disorder: allergies (Kelly & Gangur, 2009); insomnia, (Zhang & Wing, 2006); IBS, (Hungin, Chang, Locke, Dennis, & Barghout, 2005); migraine, (Lipton et

al., 2007); MS, (Pugliatti et al., 2006). This could explain why the overall rates of diagnosis for all conditions tested in both studies were significantly higher in Study 2, $t(8) = -2.8$, $p = .02$, but they were still highly correlated across our studies, $r = .83$, $p = .006$. Other important differences between cohorts (via recruitment methods) could also contribute in a way that is beyond the scope of the current study. Our aim here is to show that anxiety disorder is significantly higher in two separate studies of grapheme-colour synaesthetes, drawn from separate cohorts and tested using different methodologies.

Many people with synaesthesia superficially report no negative effects. But our evidence of elevated anxiety within grapheme-colour synaesthesia raises an important flag in considering synaesthesia as a biomarker for clinical disease. It is now possible to confirm synaesthesia in children as young as 6 years of age (Simner, Harrold, Creed, Monro, & Foulkes, 2009) and we might therefore consider whether early identification could allow the opportunity to improve life-outcomes and reduce treatment costs with respect to comorbid condition(s). The conditions studied alongside synaesthesia have significant impact on the life of the individuals affected, their families, friends and wider society in general. The financial burden, for example, with direct costs to the individual (e.g., reduced earnings) and to wider society (e.g., treatment costs, lost tax revenues) have been estimated as €1077 yearly per individual with for anxiety disorder, and €27,261 for autism (Olesen et al., 2012). We therefore suggest that even in financial terms these costs are noteworthy, and we suggest that early recognition and intervention might perhaps be possible by considering further the potential co-morbidities with synaesthesia.

Synaesthesia is not included within the DSM-5 (American Psychiatric Association, 2013) although our data might raise questions about its clinical status given its comorbidities. For health professionals, familiarity with synaesthesia might improve their understanding of the presentations of certain symptoms (e.g., anxiety) but an important consideration here is that synaesthesia is a

single label for a number of wide-ranging conditions. So one variant of synaesthesia may have comorbidities (e.g., anxiety disorder in grapheme-colour synaesthesia), while another variants may not. And there may be differences even within sub-classifications (e.g., grapheme-colour synaesthetes who experience their colours projected into space versus within the mind's eye; Dixon, Smilek, & Merikle, 2004). Finally, some variants of synaesthesia might involve disorder irrespective of any comorbidities. Synaesthesias triggering tastes, for example, can evoke negative experiences simply given the nature of the tastes themselves (e.g., vomit, earwax; e.g., Ward & Simner, 2003).

Our study could not address previous questions concerning RIS/MS and synaesthesia due to small sample sizes, and we found no link between synaesthesia and IBS (Carruthers et al., 2012) nor migraine (Jonas & Hibbard, 2015) although we did not discriminate between different headache/migraine phenomena. Another limitation of our study was that we investigated *diagnosed* health conditions only, which might have under-representation certain health conditions where people may be less likely to seek medical help. Nonetheless, this effect would be just as likely in the synaesthete group as the non-synaesthete group. Future studies might explore further this link between synaesthesia and anxiety, for example to elucidate whether particular *types of* anxiety disorders are more prevalent in grapheme-colour synaesthesia than others. In summary, our study screened a large population for synaesthesia and found that anxiety disorder increased the likelihood of having synaesthesia two-fold across both studies. Our study here aimed to open a debate about synaesthesia in a clinical context, not only for its challenging symptoms within certain variants, but also for its comorbidities within even 'benign' variants such as grapheme-colour synaesthesia.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC.

Armel, K. C., & Ramachandran, V. S. (1999). Acquired synesthesia in retinitis pigmentosa. *Neurocase*, *5*(4), 293–296. http://doi.org/10.1080/13554799908411982

Azpiroz, F., Bouin, M., Camilleri, M., Mayer, E. A., Poitras, P., Serra, J., & Spiller, R. C. (2007). Mechanisms of hypersensitivity in IBS and functional disorders. *Neurogastroenterology & Motility*, *19*, 62–88. http://doi.org/10.1111/j.1365-2982.2006.00875.x

Banissy, M. J., Cassell, J. E., Fitzpatrick, S., Ward, J., Walsh, V. X., & Muggleton, N. G. (2012). Increased positive and disorganised schizotypy in synaesthetes who experience colour from letters and tones. *Cortex*. http://doi.org/10.1016/j.cortex.2011.06.009

Banissy, M. J., & Ward, J. (2007). Mirror-touch synesthesia is linked with empathy. *Nat Neurosci*, *10*(7), 815–816. http://doi.org/10.1038/nn1926

Baron-Cohen, S., Johnson, D., Asher, J., Wheelwright, S., Fisher, S. E., Gregersen, P. K., & Allison, C. (2013). Is synaesthesia more common in autism? *Molecular Autism*, *4*(1), 40. http://doi.org/10.1186/2040-2392-4-40

Brang, D., & Ramachandran, V. S. (2008). Psychopharmacology of synesthesia; the role of serotonin S2a receptor activation. *Med Hypotheses*, *70*(4), 903–904. http://doi.org/10.1016/j.mehy.2007.09.007

Brogaard, B. (2013). Serotonergic Hyperactivity as a Potential Factor in Developmental, Acquired and Drug-Induced Synesthesia. *Frontiers in Human Neuroscience*, *7*, 657. http://doi.org/10.3389/fnhum.2013.00657

Brugha T, Cooper SA, McManus S, Purdon S, Smith J, & Scott FJ. (2012). *Estimating the prevalence of autism spectrum conditions in adults: extending the 2007 Adult Psychiatric Morbidity Survey*.

Carmichael, D. A., Down, M. P., Shillcock, R. C., Eagleman, D. M., & Simner, J. (2015). Validating a standardised test battery for synesthesia: Does the Synesthesia Battery reliably detect synesthesia? *Consciousness and Cognition*, *33*. http://doi.org/10.1016/j.concog.2015.02.001

Carruthers, H. R., Miller, V., Tarrier, N., & Whorwell, P. J. (2012). Synesthesia, Pseudo-Synesthesia, and Irritable Bowel Syndrome. *Digestive Diseases and Sciences*, *57*(6), 1629–1635. http://doi.org/10.1007/s10620-012-2054-2

Debbané, M., Van der Linden, M., Gex-Fabry, M., & Eliez, S. (2009). Cognitive and emotional associations to positive schizotypy during adolescence. *Journal of Child Psychology and Psychiatry*, *50*(3), 326–334. http://doi.org/10.1111/j.1469-7610.2008.01961.x

Dixon, M. J., Smilek, D., & Merikle, P. M. (2004). Not all synaesthetes are created equal: projector versus associator synaesthetes. *Cognitive, Affective & Behavioral Neuroscience*, *4*(3), 335–43. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15535169

Does Synaesthesia Age? Changes in the quality and consistency of synaesthetic associations. (2017). *Neuropsychologia*. http://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2017.09.013

Domschke, K., & Dannlowski, U. (2010, November). Imaging genetics of anxiety disorders. *NeuroImage*. Academic Press. http://doi.org/10.1016/j.neuroimage.2009.11.042

Duval, E. R., Javanbakht, A., & Liberzon, I. (2015). Neural circuits in anxiety and stress disorders: a focused review. *Therapeutics and Clinical Risk Management*, *11*, 115–126. http://doi.org/10.2147/tcrm.s48528

Eagleman, D. M., Kagan, A. D., Nelson, S. S., Sagaram, D., & Sarma, A. K. (2007). A standardized test battery for the study of synesthesia. *J Neurosci Methods*, *159*, 139–145. http://doi.org/10.1016/j.jneumeth.2006.07.012

Hungin, A. P. S., Chang, L., Locke, G. R., Dennis, E. H., & Barghout, V. (2005). Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Alimentary*

Pharmacology & Therapeutics, *21*(11), 1365–1375. http://doi.org/10.1111/j.1365-2036.2005.02463.x

Jacome, D. E. (1999). Volitional monocular lilliputian visual hallucinations and synesthesia. *European Neurology*, *46*, 54–56.

Janik McErlean, A. B., & Banissy, M. J. (2016). Examining the Relationship Between Schizotypy and Self-Reported Visual Imagery Vividness in Grapheme-Color Synaesthesia. *Frontiers in Psychology*, *7*(131), 1–8. http://doi.org/10.3389/fpsyg.2016.00131

Jonas, C. N., & Hibbard, P. B. (2015). Migraine in Synesthetes and Nonsynesthetes: A Prevalence Study. *Perception*, *44*(10), 1179–1202. http://doi.org/doi:10.1177/0301006615599905

Jürgens, T. P., Schulte, L. H., & May, A. (2014). Migraine trait symptoms in migraine with and without aura. *Neurology*, *82*(16), 1416–1424. http://doi.org/10.1212/wnl.0000000000000337

Kelly, C., & Gangur, V. (2009). Sex Disparity in Food Allergy: Evidence from the PubMed Database. *Journal of Allergy*, *2009*, 159845. http://doi.org/10.1155/2009/159845

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., … Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry*, *51*(1), 8–19. http://doi.org/10.1001/archpsyc.1994.03950010008002

Lewandowski, K. E., Barrantes-Vidal, N., Nelson-Gray, R. O., Clancy, C., Kepley, H. O., & Kwapil, T. R. (2006). Anxiety and depression symptoms in psychometrically identified schizotypy. *Schizophrenia Research*, *83*(2), 225–235. http://doi.org/http://dx.doi.org/10.1016/j.schres.2005.11.024

Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M. L., & Stewart, W. F. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, *68*(5),

343–349. http://doi.org/10.1212/01.wnl.0000252808.97649.21

Luke, D., & Terhune, D. (2013). The induction of synaesthesia with chemical agents: a systematic review. *Frontiers in Psychology*, *4*, 753. http://doi.org/10.3389/fpsyg.2013.00753

Martín-Merino, E., Ruigómez, A., Wallander, M.-A., Johansson, S., & García-Rodríguez, L. A. (2010). Prevalence, incidence, morbidity and treatment patterns in a cohort of patients diagnosed with anxiety in UK primary care. *Family Practice*, *27*(1), 9–16. http://doi.org/10.1093/fampra/cmp071

Mason, O., & Claridge, G. (2006). The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): Further description and extended norms. *Schizophrenia Research*, *82*(2), 203–211. http://doi.org/http://dx.doi.org/10.1016/j.schres.2005.12.845

McLean, C. P., Asnaani, A., Litz, B. T., & Hofmann, S. G. (2011). Gender differences in anxiety disorders: Prevalence, course of illness, comorbidity and burden of illness. *Journal of Psychiatric Research*, *45*(8), 1027–1035. http://doi.org/http://dx.doi.org/10.1016/j.jpsychires.2011.03.006

McManus, S., Bebbington P, Jenkins R, & T., B. (2016). *Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014*. Leeds.: Leeds: NHS Digital.

Neufeld, J., Roy, M., Zapf, A., Sinke, C., Emrich, H. M., Prox-Vagedes, V., … Zedler, M. (2013a). Is synesthesia more common in patients with Asperger syndrome? *Frontiers in Human Neuroscience*, *7*, 847. http://doi.org/10.3389/fnhum.2013.00847

Neufeld, J., Roy, M., Zapf, A., Sinke, C., Emrich, H. M., Prox-Vagedes, V., … Zedler, M. (2013b). Is synesthesia more common in patients with Asperger syndrome? *Frontiers in Human Neuroscience*, *7*, 847. http://doi.org/10.3389/fnhum.2013.00847

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., Jönsson, B., on behalf of the, C. study group, & the European Brain, C. (2012). The economic cost of brain disorders in Europe.

European Journal of Neurology, *19*(1), 155–162. http://doi.org/10.1111/j.1468-1331.2011.03590.x

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Mol Psychiatry*, *21*(10), 1485. http://doi.org/10.1038/mp.2016.11

Pugliatti, M., Rosati, G., Carton, H., Riise, T., Drulovic, J., Vécsei, L., & Milanov, I. (2006). The epidemiology of multiple sclerosis in Europe. *European Journal of Neurology*, *13*(7), 700–722. http://doi.org/10.1111/j.1468-1331.2006.01342.x

Ramachandran, V. S., & Hubbard, E. M. (2001). Psychophysical investigations into the neural basis of synaesthesia. *Proc R Soc London B*, *268*, 979–983. http://doi.org/10.1098/rspb.2000.1576

Rich, A. N., Bradshaw, J. L., & Mattingley, J. B. (2005). A systematic, large-scale study of synaesthesia: implications for the role of early experience in lexical-colour associations. *Cognition*, *98*, 53–84. http://doi.org/10.1016/j.cognition.2004.11.003

Rothen, N., Meier, B., & Ward, J. (2012). Enhanced memory ability: Insights from synaesthesia. *Neuroscience & Biobehavioral Reviews*, *36*(8), 1952–1963. http://doi.org/http://dx.doi.org/10.1016/j.neubiorev.2012.05.004

Rothen, N., Seth, A. K., Witzel, C., & Ward, J. (2013). Diagnosing synaesthesia with online colour pickers: Maximising sensitivity and specificity. *Journal of Neuroscience Methods*, *215*(1), 156–160. http://doi.org/http://dx.doi.org/10.1016/j.jneumeth.2013.02.009

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychon Bull Rev*, *16*(2), 225–237. http://doi.org/10.3758/pbr.16.2.225

Simner, J. (2012). Defining synaesthesia. *Br J Psychol*, *103*(1), 1–15. http://doi.org/10.1348/000712610x528305

Simner, J., & Bain, A. E. (2017). Do children with grapheme-colour synaesthesia show cognitive benefits? *British Journal of Psychology*. http://doi.org/10.1111/bjop.12248

Simner, J., & Bain, A. E. (2018). Do children with grapheme-colour synaesthesia show cognitive benefits? *British Journal of Psychology*, *109*(1). http://doi.org/10.1111/bjop.12248

Simner, J., & Carmichael, D. (2015). Is synaesthesia a dominantly female trait? *Cognitive Neuroscience*, *6*(2–3), 68–76. http://doi.org/10.1080/17588928.2015.1019441

Simner, J., Carmichael, D. A., Hubbard, E. M., Morris, Z., & Lawrie, S. M. (2015). Rates of white matter hyperintensities compatible with the radiological profile of multiple sclerosis within self-referred synesthete populations. *Neurocase*, *21*(3), 322–330. http://doi.org/10.1080/13554794.2014.892625

Simner, J., Harrold, J., Creed, H., Monro, L., & Foulkes, L. (2009). Early detection of markers for synaesthesia in childhood populations. *Brain*, *132*(1), 57–64. http://doi.org/10.1093/brain/awn292

Simner, J., Mulvenna, C., Sagiv, N., Tsakanikos, E., Witherby, S. A., Fraser, C., … Ward, J. (2006). Synaesthesia: the prevalence of atypical cross-modal experiences. *Perception*, *35*, 1024–1033. http://doi.org/10.1068/p5469

Simner, J., Mulvenna, C., Sagiv, N., Tsakanikos, E., Witherby, S. A., Fraser, C., … Ward, J. (2006). Synaesthesia: The prevalence of atypical cross-modal experiences. *Perception*, *35*(8). http://doi.org/10.1068/p5469

Simner, J., Rehme, M. K., Carmichael, D. A., Bastin, M. E., Sprooten, E., McIntosh, A. M., … Zedler, M. (2016). Social responsiveness to inanimate entities: Altered white matter in a 'social synaesthesia.' *Neuropsychologia*, *91*. http://doi.org/10.1016/j.neuropsychologia.2016.08.020

Simner, J., & Ward, J. (2006). Synaesthesia: The taste of words on the tip of the tongue. *Nature*, *444*(7118), 438. http://doi.org/10.1038/444438a

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(8), 921–929. http://doi.org/http://dx.doi.org/10.1097/CHI.0b013e318179964f

Terluin, B., Oosterbaan, D. B., Brouwers, E. P. M., van Straten, A., van de Ven, P. M., Langerak, W., & van Marwijk, H. W. J. (2014). To what extent does the anxiety scale of the Four-Dimensional Symptom Questionnaire (4DSQ) detect specific types of anxiety disorder in primary care? A psychometric study. *BMC Psychiatry*, *14*(1), 121. http://doi.org/10.1186/1471-244x-14-121

Tyrer, P., & Baldwin, D. (2006). Generalised anxiety disorder. *The Lancet*, *368*(9553), 2156–2166. http://doi.org/10.1016/S0140-6736(06)69865-6

Wang, W., Qian, S., Liu, K., Li, B., Li, M., Xin, K., & Sun, G. (2016). Reduced white matter integrity and its correlation with clinical symptom in first-episode, treatment-naive generalized anxiety disorder. *Behavioural Brain Research*, *314*, 159–164. http://doi.org/10.1016/j.bbr.2016.08.017

Ward, J., Huckstep, B., & Tsakanikos, E. (2006). Sound-colour synaesthesia: to what extent does it use cross-modal mechanisms common to us all? *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *42*(2), 264–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16683501

Ward, J., & Simner, J. (2003). Lexical-gustatory synaesthesia: Linguistic and conceptual factors. *Cognition*, *89*(3), 237–261. http://doi.org/10.1016/S0010-0277(03)00122-7

Ward, J., Thompson-Lake, D., Ely, R., & Kaminski, F. (2008). Synaesthesia, creativity and art: what is the link? *Br J Psychol*, *99*(Pt 1), 127–141. http://doi.org/10.1348/000712607x204164

Whitaker, K. J., Kang, X., Herron, T. J., Woods, D. L., Robertson, L. C., & Alvarez, B. D. (2014). White matter microstructure throughout the brain correlates with visual imagery in grapheme–color synesthesia. *NeuroImage*, *90*, 52–59. http://doi.org/https://doi.org/10.1016/j.neuroimage.2013.12.054

Zhang, B., & Wing, Y.-K. (2006). Sex Differences in Insomnia: A Meta-Analysis. *Sleep*, *29*(1), 85–93. http://doi.org/10.1093/sleep/29.1.85

	Binary Logistic Regression Model			
	Model 1		Model 2	
Predictors	*β* coefficient	Odds ratio	*β* coefficient	Odds ratio
Intercept	-4.46***	*NA*	-4.44***	NA
Age Age, quadratic	-.10*** .002*	.90 1.002	-.10*** .002*	.90 1.002
Anxiety disorder ASC OCD	.60[#] 1.28[##] 1.65***	1.82 3.60 5.23	*.64*[#] *nf* 1.65***	*1.91* *nf* 5.22
Chi (df) p R Square (N)	58.97 (5) *** .07		56.97 (4) *** .07	

N = Nagelkerke;[##]*p* = .10 (*β*1.28, *p* = .10); [#]*p* < .10 (*β* 0.60, *p* = .086; *β* 0.64, *p* = .06); * *p* < .05; ***p* < .01; ****p* < .001. *NA* = Not applicable; *nf* =not fitted.

Table 1. Output of binary logistic regression models 1 and 2 (Study 1) predicting synaesthetic status, given the predictors shown in column 1.

	Binary Logistic Regression Model	
Predictors	*β* coefficient	Odds ratio
Intercept	-1.370** (*p* = .004)	*NA*
Sex	1.041* (*p* = .030)	2.8
Allergies Anxiety disorder ASC OCD	-0.27 (*p* = .307) .68* (*p* = .015) 1.82 (*p* = .139) -0.85 (*p* = .111)	0.76 1.97 6.19 0.43
Chi (df) p R Square (N)	16.5 (5)** (*p* = .006) .08	

N = Nagelkerke; * *p* < .05; **p < .01; ***p < .001. *NA* = Not applicable; *nf* =not fitted.

Table 2. Output of binary logistic regression model predicting synaesthetic status, given the predictors shown in column 1 (Study 2).

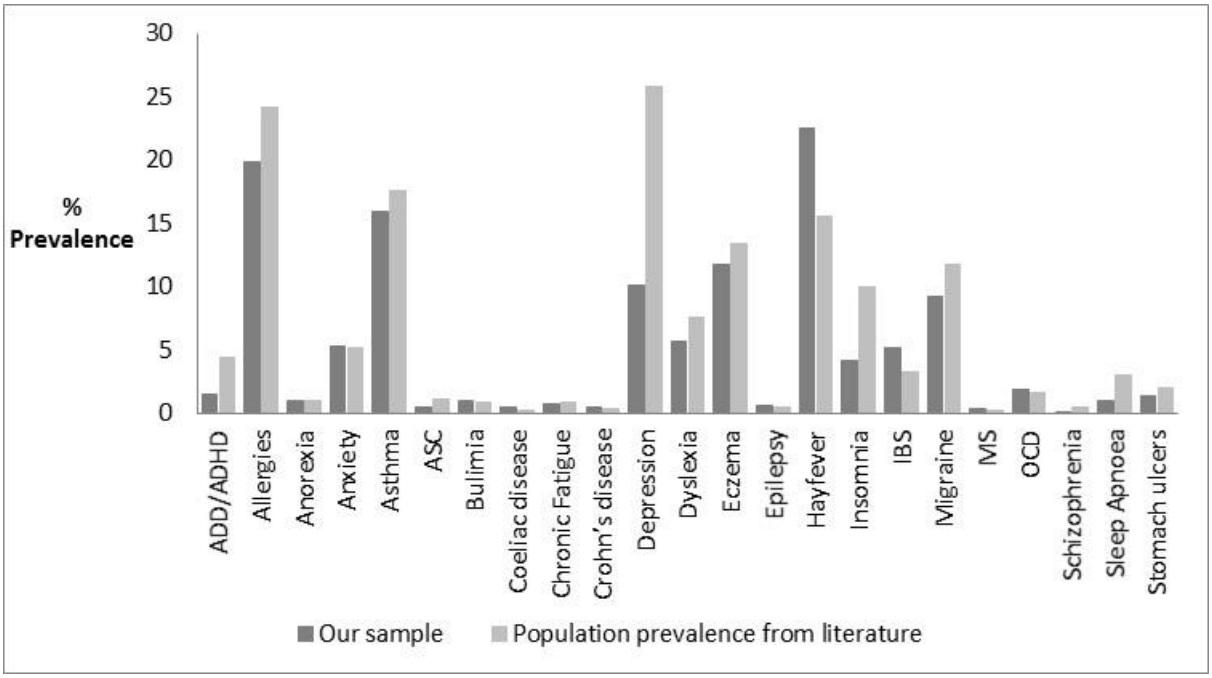

Figure 1. **Prevalence of health conditions** Shows the percent (%) prevalence of each of the 23 conditions of interest in our study. Dark grey bars represent our testing sample and are self-declared rates of diagnosis within the lifetime; light grey bars represent the general population, taken from published epidemiology studies described in Table 1 (supplementary material).