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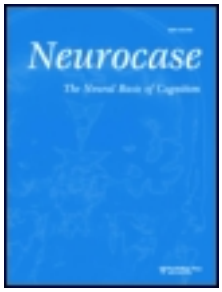

Neurocase: The Neural Basis of Cognition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/nncs20

Rates of white matter hyperintensities compatible with the radiological profile of multiple sclerosis within self-referred synesthete populations

Julia Simner[a], Duncan A. Carmichael[abc], Edward M. Hubbard[d], Zoe Morris[e] & Stephen M. Lawrie[c]

[a] Department of Psychology, University of Edinburgh, Edinburgh, UK
[b] Institute for Adaptive and Neural Computation, University of Edinburgh, Edinburgh, UK
[c] Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK
[d] Department of Educational Psychology, University of Wisconsin-Madison, Madison, UK
[e] Division of Clinical Neurosciences, Western General Hospital, Edinburgh, UK
Published online: 05 Mar 2014.

To cite this article: Julia Simner, Duncan A. Carmichael, Edward M. Hubbard, Zoe Morris & Stephen M. Lawrie (2014): Rates of white matter hyperintensities compatible with the radiological profile of multiple sclerosis within self-referred synesthete populations, Neurocase: The Neural Basis of Cognition, DOI: 10.1080/13554794.2014.892625

To link to this article: http://dx.doi.org/10.1080/13554794.2014.892625

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Neurocase, 2014
http://dx.doi.org/10.1080/13554794.2014.892625

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Rates of white matter hyperintensities compatible with the radiological profile of multiple sclerosis within self-referred synesthete populations

Julia Simner[a]*, Duncan A. Carmichael[a,b,c], Edward M. Hubbard[d], Zoe Morris[e] and Stephen M. Lawrie[c]

[a]*Department of Psychology, University of Edinburgh, Edinburgh, UK;* [b]*Institute for Adaptive and Neural Computation, University of Edinburgh, Edinburgh, UK;* [c]*Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK;* [d]*Department of Educational Psychology, University of Wisconsin-Madison, Madison, UK;* [e]*Division of Clinical Neurosciences, Western General Hospital, Edinburgh, UK*

(*Received 1 October 2013; accepted 28 January 2014*)

Synesthesia is an inherited condition causing unusual secondary sensations (e.g, sounds might be experienced as both auditory and visual percepts). The condition has been linked with cognitive and perceptual benefits and is considered a benign alternative form of perception. Here, we investigate self-referred synesthete populations and their rates of radiologically determined white matter hyperintensities (WMH) of a type compatible with the McDonald imaging criteria for the diagnosis of multiple sclerosis (MS). MS is a chronic condition resulting in damage to myelination surrounding nerve fibers of the central nervous system (CNS). Magnetic resonance imaging (MRI) features highly suggestive of MS without overt clinical symptoms are termed *radiologically isolated syndrome* (RIS). We present data showing that the shared MRI profile of MS and RIS has been significantly overrepresented in synesthetes who have participated in neuroimaging research. We present validation of the clinical and MRI status of these synesthetes and an analysis showing the significant probability their unusual numbers may not have arisen by chance. We discuss how to interpret significant data based on small case numbers and consider the implications of our findings for synesthesia's clinical status.

Keywords: synaesthesia; synesthesia; multiple sclerosis; radiologically isolated syndrome; comorbidity

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For people with synesthesia, stimuli are experienced with unusual secondary associations. For example, sound-color synesthetes experience sound stimuli as accompanied by both auditory and visual (i.e., color) percepts (Asher et al., 2009). Synesthesia tends to be regarded in positive rather than negative terms and has a range of cognitive and perceptual benefits (e.g., for memory; Yaro & Ward, 2007). Here, we investigate an observation of unusually high rates of white matter hyperintensities (WMH) in a group of synesthetes. These hyperintensities are areas of high intensity on T2-weighted magnetic resonance imaging (MRI) scans of a type compatible with the McDonald (imaging) criteria for the diagnosis of multiple sclerosis (MS; Polman et al., 2011).

MS is an inflammatory disease of the central nervous system (CNS) with a broad range of perceptual and motor symptoms. It is thought to be caused by environmental risk factors in combination with genetic susceptibility (Compston & Coles, 2008). MS is characterized by demyelination, axonal loss, and gliosis of white matter (Weiner, 2009). Diffusion tensor imaging (DTI) shows reduced fractional anisotropy (FA) scores in MS patients, indicating reduced white matter integrity in lesion sites and elsewhere (Roosendaal et al., 2009). Although MS is typically classified as a white matter disorder, gray matter is also affected, with reduced volume common in several areas (Ceccarelli et al., 2008). If patients present with MRI features suggestive of MS but without overt clinical symptoms, this is termed *radiologically isolated syndrome* (RIS). From a radiological perspective, MRI scans of RIS and MS are indistinguishable, and it is only the presence of clinical symptoms that differentiates between the two conditions. There is also a clinical relationship between the conditions in that approximately one-third of patients with RIS develop MS symptoms within 2–5 years (Granberg, Martola, Kristoffersen-Wiberg, Aspelin, & Fredrikson, 2013).

Structural differences in white and gray matter also characterize the condition of synesthesia. Synesthetes show both increases and decreases in gray matter volume (Hänggi, Beeli, Oechslin, & Jäncke, 2008; Jäncke, Beeli, Eulig, & Hänggi, 2009) and altered coherence of white matter (Hänggi, Wotruba, & Jancke, 2011; Jäncke et al., 2009; Rouw & Scholte, 2007). This altered white matter is found in regions implicated by the synesthetic report and also elsewhere. For example, synesthetes experiencing

*Corresponding author. Email: j.simner@ed.ac.uk
JS and DAC contributed equally to this work. JS and EMH conceived the project; JS and DAC wrote the paper with team feedback; JS, DAC, EMH and SML gathered data, ZM assessed and interpreted neuroradiological data, and JS and DAC conducted the statistical analyses.

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color sensations show increased FA compared with controls near color selective region V4 (Rouw & Scholte, 2007) but also show FA increases (Rouw & Scholte, 2007) and decreases (Hänggi et al., 2008) in parietal lobe. The cortical reorganization of white and gray matter in synesthesia might call for comparison with MS-RIS, and we discuss in this article whether epidemiological or pathological links might exist between them.

Our question is motivated by a particularly high occurrence of MRI abnormalities consistent with the neuroradiological profile of MS-RIS within synesthetes who have presented to our laboratories for brain imaging studies. In three independent synesthete cohorts across three countries (San Diego, CA, United States; Paris, France; and Edinburgh, United Kingdom), we have opportunistically found clinical and radiological indicators suggestive of MS in 1 in 6 synesthetes, 1 in 10 synesthetes, and 1 in 13 synesthetes, respectively. Our studies were not initiated with the intention of investigating the prevalence of MS-RIS, but our unexpected findings have led us to evaluate the post hoc detection of white matter abnormalities in these three participants. All three affected cases met the McDonald (imaging) criteria for the diagnosis of MS. Subject 1 (United States) has a full diagnosis of MS, while Subjects 2 (France) and 3 (United Kingdom) are currently free from clinical symptoms and therefore considered to have RIS. Subjects 2 and 3 were initially flagged by routine protocols in our studies in which neuroradiologists examine T2-weighted axial MRI scans for unanticipated pathology. Subject 1's diagnosis was first suggested by her general practitioner several months after our study, because routine radiological checks were not part of that study's protocol.

Our finding of three cases of MS-RIS among 29 synesthetes is suggestive of an unusually high rate. However, we must address the possibility that we have inadvertently focused on just those studies where anomalies were found, rather than all synesthesia imaging studies to date. Collectively, 29 published studies (see Table 2) have scanned 211 synesthetes (including 6 of our own 29 synesthetes, described in Hubbard, Arman, Ramachandran, & Boynton, 2005). Together with our remaining unpublished cases (N = 23), this gives 234 synesthete scans in existence known to us. Outside our cohort of 29 participants, we have been able to ascertain that 80 additional synesthetes' MRI scans were checked with a similar radiologist protocol, and none revealed anomalous findings of this type.[1] A further 121 were scanned without this protocol and the remaining four scans have an unknown status. The most conservative approach is to assume no cases of pathology in any of the 234 scanned cases, other than the three identified here. Our methodology discussed later is to evaluate this occurrence of MS-RIS in synesthetes against appropriate baselines. We first begin with full case descriptions of the three affected synesthetes. This is followed by a set of analyses that consider the appropriate baselines against which to compare our finding of three affected cases (1 MS; 2 RIS). To anticipate our methodologies discussed later, we take the most stringent standards against which to compare our observations (given factors such as the geographic variability of MS and the sampling method of our studies) and nonetheless find that the number of affected cases is significantly higher than chance would predict.

Empirical study

In this section, we evaluate our three cases of MS-RIS both qualitatively and quantitatively, beginning with a detailed clinical evaluation.

Case details of affected synesthetes

Synesthesia status

Table 1 shows the synesthetic status and demographic background of the three synesthete participants in whom radiological anomalies have been identified. The table shows their synesthesia phenotypes, and these comprise the following: *grapheme-color synesthesia* gives rise to colored percepts triggered by letters or digits (e.g., the letter *A* might be red; Asher et al., 2009); *sequence-*

Table 1. Synesthetic Case Descriptions.

Test site	Age	Sex	Nationality	Synesthesia phenotype(s)*	MS-RIS?
San Diego	26	Female	American	Grapheme-color	MS
Paris	25	Female	French	Number-space, time-space (colored), grapheme-color	RIS
Edinburgh	31	Female	British/English	Sequence-personality, letter-space, numbers-space, time-space	RIS

*Verification of synesthesia relies on the behavioral "gold standard" test for synesthesia, which assesses the consistency of the synesthetic report over time (e.g., Eagleman, Kagan, Nelson, Sagaram, & Sarma, 2007; Simner et al., 2006). In this, participants are required to first report their synesthetic experiences for a list of provided stimuli (e.g., they report their colors for a list of letters), and they are subsequently retested after some considerable time (e.g., 6 months, for the case scanned in San Diego; see Hubbard et al., 2005 for methodological details). Synesthetes are identified as those who are significantly more consistent in their reports over time, compared to a group of matched controls who invent/recall analogous associations.

Note: For each affected synesthete, the table shows the imaging lab testing site, the participant's age at scanning, sex, country of origin, verified synesthesia phenotype(s), and the clinical status.

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personality synesthesia gives rise to complex personifications triggered by the members of linguistic sequences (e.g., *Monday* might be "female, unfriendly"; Simner & Holenstein, 2007); *number-space synesthesia*, *letter-space synesthesia* and *time-space synesthesia* are all variants of the broader category of *sequence-space synesthesia*, in which linguistic sequences are perceived in spatial arrays (e.g., the letters A–Z might extend in an undulating line from right to left across the visual field; see Simner, 2009 for review).

Clinical status of MS-RIS

All three synesthete participants in question met the McDonald (imaging) criteria for the diagnosis of MS. This requires the presence of one or more T2-weighted high signal lesions in at least two of the following four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord. A full diagnosis of MS has been given in the case of one participant, while the other two subjects are currently free from clinical symptoms and are therefore considered to have RIS. The synesthetic status of each participant is shown in Table 1 and their clinical status is described here.

Subject 1 (San Diego, CA, United States) was diagnosed with clinically definite relapsing-remitting MS several months after taking part in a synesthesia study in 2001. A diagnosis of MS was first suggested by this participant's general practitioner because routine radiological checks were not part of the study's protocol. Subsequent neurological follow-up consisting of sagittal and axial T1-weighted FLAIR and axial T2-weighted and axial and coronal T1-weighted MRI scans revealed extensive hyperintensities in both the brain and cervical spine, considered to be pathognomonic for MS. These white matter lesions, in conjunction with history of clinical symptoms, confirmed this participant's diagnosis of MS. This participant had a total of 16 lesions, in both periventricular and juxtacortical white matter (see Figure 1). Periventricular lesions were located in the corpus callosum and in occipital and parietal areas. Juxtacortical lesions were found in the parietal region. Lesions were also detected in the spinal cord. This subject was originally scanned for, but subsequently excluded from, Hubbard et al. (2005) (see Table 2).

Subject 2 (Paris, France) participated in synesthesia research in 2006, where her axial T2-weighted MRI scan was reviewed as part of routine assessments for unanticipated pathology by a consultant neuroradiologist. Initial examination of her resultant T2-weighted MRI scan revealed WMH in the brain. A second, axial T2-weighted FLAIR MRI scan, obtained 2 years after the initial scan, confirmed the presence of white matter lesions, judged to be consistent with McDonald criteria (see Figure 2). Due to a lack of progression, these lesions are considered stable and this participant has remained free of clinical symptoms. This participant had more than 20 identified lesions in periventricular and juxtacortical white matter. Periventricular lesions were in frontal and parietal areas, while juxtacortical lesions were distributed across frontal, parietal, and temporal regions. This subject was scanned for Hubbard et al. (unpublished data) (see Table 2).

Figure 1. Axial T2-weighted image showing a left parietal ovoid periventricular lesion (of 16 overall lesions), from subject 1.

Subject 3 (Edinburgh, United Kingdom) participated in synesthesia research in 2008 and her resultant axial T2-weighted MRI scan was also examined routinely by a consultant radiologist to detect unanticipated pathology. Initial examination revealed WMH in the brain of this subject. This T2-weighted MRI scan was independently examined by a second neuroradiologist who confirmed that the number and location of the white matter lesions met the McDonald imaging criteria for diagnosis of MS (see Figure 3). Again, this participant has remained free of clinical symptoms since the initial presentation of her abnormal scan. This participant had more than 20 lesions in periventricular and juxtacortical white matter (see Figure 3). Periventricular lesions were found in frontal, parietal, temporal, and occipital areas. Juxtacortical lesions were identified in temporal and parietal areas. Infratentorial lesions were also present. This subject was scanned for, and subsequently excluded from, a study by Rehme et al. (in review) (see Table 2).

Case details of all synesthetes with existing MRI scans

Table 2 shows what is to our knowledge all studies that have generated MRI scans from synesthete participants at the time of writing including all published studies, plus our two unpublished samples. Published articles were

Table 2. MRI studies of synesthete participants.

Year	Authors	Total number of participants (*N*)	Status‡‡	Number of female participants (*N*)
European studies				
2001	Aleman et al.	1	¥	1
2001	Weiss et al.	1	†	1
2005	Weiss et al.	9	†	6
2006	Hubbard et al. (unpublished data)	10	§	10
2006	Sperling et al.	4		4
2007	Rouw and Scholte	0*		0
2008	Hänggi et al.	1	¥	1
2009	Jäncke et al.	0*		0
2009	Weiss and Fink	16*	†	15
2010	Rouw and Scholte	42	¥	42
2010	van Leeuwen et al.	21	¥	19
2011	Gaschler-Markefski et al.	7	¥	6
2011	Hänggi et al.	24	¥	20
2011	Specht and Laeng	2	††	2
2011	van Leeuwen et al.	0*		0
2012	Dovern et al.	5*	†	5
2012	Hupe et al.	10	¥	7
2012	Neufeld et al.	14	¥	9
UK studies				
2002	Nunn et al.	13	††	13
2005	Blakemore et al.	1	††	1
2006	Gray et al.	2*	††	2
2007	Cohen Kadosh et al.	1	††	0
2008	Bor et al.	1	††	0
2008	Tang et al.	10	††	8
2011	Jones et al.	2	†† ¶	1
2012	Banissy et al	9	†	5
2013	Rehme et al. (under review)	13	§	13
N. American studies				
2003	Elias et al.	1	¥	1
2005	Hubbard et al.	6	§	3
2012	Brogaard et al.	1	††	0
Other studies				
2006	Rich et al.	7	††	6
	Total	234		201

*Subject numbers have been adjusted to exclude duplicate participants already scanned in previous studies by the same group (shown elsewhere in the table).
†Routine radiological checks for pathology performed by neurologist and no anomalies found.
††Routine radiological checks carried out by a neuroradiologist and no anomalies found.
§Members of our study cohort (i.e., studies directed in our labs); three anomalies in $N = 29$ scans.
¶A study directed by colleagues outside our labs, but JS coauthoring.
¥No routine radiological checks for pathology performed.
‡‡Status with respect to radiological anomalies (see the previous footnotes; unknown unless otherwise stated).

retrieved from an all-years search of PubMed using search terms "syn*esthesia" (UK/US spellings) and "MRI", and any additional details on participants given in the following discussion that were not available in the literature were retrieved by contact with the authors of these studies.

Analysis of the prevalence of MS-RIS cases among scanned synesthetes against expected baselines

We found three cases of MS-RIS in 234 synesthetes who were self-referred for brain scanning studies across the literature. To establish whether the number of affected synesthetes is statistically significant, we must compare the prevalence of observed cases against a meaningful baseline. Since RIS and MS are indistinguishable, from a radiological perspective, we first consider all three cases as a unified phenomenon. Then, since RIS and MS are different in a clinical/symptomatic sense, we additionally consider the two cases of RIS as a distinct phenomenon. Methodologically speaking, we will take our RIS baseline from a meta-analysis of the prevalence of RIS across all MRI scans described in the imaging literature (and later we describe our very conservative approach in this regard). We will take our MS baselines from rates reported

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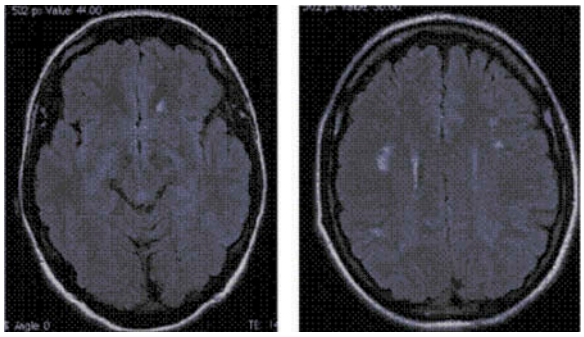

Figure 2. Axial T2-weighted FLAIR images showing (left) a left frontal periventricular lesion and (right) multiple lesions; the right parietal lesion involves juxtacortical U fibers. [To view this figure in color, please see the online version of this Journal.]

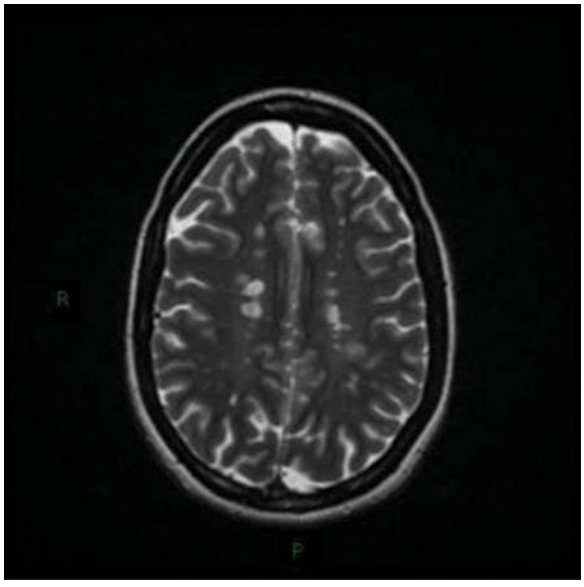

Figure 3. Axial T2-weighted image showing multiple ovoid periventricular white matter lesions, from subject 3.

in clinical prevalence studies. Since the prevalence of MS is sex-linked and geographically variable, we have considered that the large majority of all scanned synesthetes are female (86%) and have come from studies conducted in Europe (94%). Accordingly, we took a female MS prevalence figure for Europe. Again however, since a key aim was to be maximally conservative (i.e., to compare our findings with the highest prevalence rates where possible), we additionally reanalyzed our data using the most stringent prevalence rate according to the nationality of the three affected cases (American/French/English). In other words, since the rate of MS is highest in England (vs. America or France), we used this highest England baseline in a second analysis. In the following we describe these baseline selection procedures in more detail and the resultant statistical outcomes of our analyses (showing whether MS-RIS is indeed significantly higher in self-referred synesthete samples).

Baseline selection and results

There is no published combined prevalence of MS-RIS, so we use an additive value from each separately. Our recent meta-analysis (Morris et al., 2009) shows a baseline of RIS in the general population of 57.8/100,000. This figure was based on nine cases of unanticipated WMH considered as definite demyelination, which were found in 15,559 scans reported in the literature. To be conservative here, we will also include three cases of *possible* demyelination in that meta-analysis, and furthermore, we will consider scans only from self-referred volunteer research participants (giving a total of 12 RIS cases found in 8,441 research scans; Proportion (P) = 0.14%, 95% CI [0.08%, 0.25%]; Morris et al., 2009). We consider only self-referred volunteers because this type of participant is similar to those in our own cohort of synesthetes and across the 234 scanned synesthetes more widely. It is important to consider this method of self-referral since it might increase the number of RIS cases in our cohort. Specifically, self-referred/volunteer recruitment in any brain imaging study may increase rates of neuropathology by over-recruitment of participants who are seeking covert evaluation for undeclared neurological complaints (Morris et al., 2009). In other words, our three affected synesthetes may have volunteered for our studies to assuage personal neurological concerns, and we must therefore compare their number against a baseline that specifically takes this into account. In summary, all these considerations give us a comparative baseline for RIS in the general population of 142/100,000. However, we point out that this baseline is likely to be highly inflated since closer inspection of the data that contributed to our meta-analysis reveals that two-thirds of cases contributing to this figure were found in a single study in which 90.0% of participants were former lead workers with a mean age of 60.1 years (Alphs, Schwartz, Stewart, & Yousem, 2006). Since the likelihood of detecting WMH increases significantly with age (Smith, Snowdon, Wang, & Markesbery, 2000) and with exposure to neurotoxicants such as lead (Stewart et al., 2006), the true prevalence of WMH in the general population of self-referred volunteers is likely to be substantially lower than the baseline we are selecting here. Nonetheless, we use this baseline as a maximally conservative estimate (to combine with a suitable estimate for MS prevalence below), for comparison with our synesthete sample.

The prevalence of MS in the general population is better understood and known to vary by geographic region (with particularly high rates in Scotland, Sutherland, 1956, and by sex: females approximately 2:1; Pugliatti et al., 2006). This is of note given our Edinburgh testing study

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(in which 4 of 13 participants were Scottish; the remainder traveled from England) and the fact that the scanned synesthesia population is skewed towards females (F = 201) – as potentially, is synesthesia in general (e.g., see Ward & Simner, 2005). Considering the sex and nationality of the 234 scanned synesthetes (using the location of testing centers as an indicator of nationality for cases unknown to us), an appropriate baseline is the rate of MS in female Europeans (110/100,000[2]) since synesthetes were virtually exclusively European (94%, N = 220; including four Scots, none of whom showed pathology). This we combined with the baseline for RIS to give an additive RIS-MS baseline of 252/100,000.

Using the exact binomial test, we calculated the probability of obtaining our observed number of MS-RIS cases within scanned synesthetes, given the expected baseline prevalence estimates generated earlier. Thus, we estimated the probability of three observations of MS-RIS among 234 self-referred synesthetes (Proportion (P) = 1.3%, 95% binomial CI [0.3%, 3.7%]; 1282/100,000) given an expected population prevalence of 252/100,000. Our statistical test shows this rate among synesthetes to be significantly higher than chance might predict (p = 0.02). This difference remains significant (p = 0.04) even if we substitute the female Europe MS rate and use instead the female England MS rate,[3] as the most extremely conservative option given the demographics of our three affected cases (American/French/English).

Combining our three cases has allowed us to consider the shared MRI profile of MS and RIS and their related clinical progression (Granberg et al., 2013). However, we might alternatively exclude our case of MS as a separate phenomenon and consider only our two observations of RIS against all 103 scans with protocols to check for such anomaly (P = 1.9%, 95% binomial CI [0.2%, 6.7%]). Taking again our highest RIS baseline (142/100,000), this finding is also highly significant (p = 0.01). Indeed, taking even the most extreme assumption of no other cases in any synesthete scanned to date – checked or unchecked – an observation of two cases in 234 (P = 0.9%; binomial CI [0.1%, 3.1%]) remains significant (p = 0.04).[4]

Discussion

We initially observed three cases showing WMH compatible with the radiological profile of MS – one case of MS and two of RIS – in 29 synesthetes from three of our imaging labs across three different countries. We have taken the most conservative approach in assuming no further cases in any synesthetes scanned to date, placing the prevalence at 3 affected cases in 234 synesthetes (1,282/100,000, compared to a population baseline estimate of 252/100,000). Two cases of RIS in 103 brain scans checked for pathologies would, if representative, place the prevalence of RIS in synesthetes at 1,942/100,000 (compared to a baseline of 142/100,000). These rates are significantly higher than expectation, even against our highly conservative baselines. We also specifically controlled for the possibility that our three affected cases may have volunteered for our studies to assuage personal neurological concerns. We did this by comparing our RIS cases to a baseline constructed only from studies that included similar, self-referred, volunteer participants. In other words, we compared our rates to studies likely to have just as many "concerned self-referrers" as our own, rather than to studies using nonvoluntary recruitment methods (e.g., work-related health screening; Weber & Knopf, 2004).

We would like to very clearly acknowledge that we report only a small number of affected cases, and we evidently do not claim that synesthesia causes MS-RIS. Indeed, our small sample size means we hold back from making any strong claim whatsoever about links between these two conditions. There are many environmental factors thought to contribute to the development of MS and RIS; the evidence we present here suggests having synesthesia may be one factor that could merit further investigation. Indeed, we have chosen to present our data for two reasons. The first is that the rates we have found are statistically significant; a considerably greater sample size would usually be needed to detect the numbers we have found – although again our sample sizes are small. The second reason we present our data is a practical one: cases of pathology are usually excluded from MRI study populations as soon as they are detected. Therefore, they often do not appear in the literature and so remain unknown outside the research group. We have published our data because we judge it important that other researchers working in this area are aware of our cases, and so might not overlook future neurological abnormalities, should they ever be discovered. If a meaningful link between synesthesia and MS did exist, and as scanning of synesthetes for research purposes becomes more commonplace, further cases of this nature would arise, and so we encourage researchers to make any cases known to the wider community if they share similarities with our own.

One explanation for a link between synesthesia and MS could be the occurrence of synesthesia-like symptoms *after* the onset of MS. In other words, it is possible that the degenerative neurological damage caused by MS might give rise to sensory disorders that *mimic* synesthesia, while having different causes. Sensory disturbances do accompany MS (e.g., changes in color vision; Gregori, Papazachariadis, Farruggia, & Accornero, 2011) although this hypothesis would imply that the onset of synesthesia-like symptoms should be later in life – resulting from MS-related changes in brain structure. However, we do not believe this accounts for the cases we present here and for two reasons. Later-acquired synesthesias are qualitatively different to developmental variants (Ward, 2013) and do

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not reflect the synesthesias of our participants. Acquired variants of synesthesia tend to involve low-level sensory triggers (e.g., tones) rather than learned symbols such as graphemes (Ward, 2013) although it is precisely this latter type of trigger (graphemes etc.) that our own cases possess – and which might therefore be considered a hallmark of developmental synesthesia. Furthermore, all three of our cases report life-long synesthesia, stemming back from early childhood, and being present for as long as they can remember.

Finally, we point out one recent finding that might be considered alongside our own. Bashir, Lipton, Ashina, and Ashina (2013) have shown white matter abnormalities in people suffering migraine, especially those for whom the migraine is accompanied by auras. Migraine has been linked with synesthesia (e.g., Alstadhaug & Benjaminsen, 2010) and the auras associated with migraine are visual disturbances that themselves might be considered as resembling certain types of synesthetic sensations (e.g., colored photisms). Future studies might therefore further explore any possible links between synesthesia and migraine and the types of visual disturbances they each engender.

In conclusion to the current study, we have demonstrated an apparent statistical link between MS-RIS and synesthesia. Overall, we have been conservative in our study in three ways: we selected baselines in an overly conservative way, we took additional measures to be conservative when conducting our statistical analysis (e.g., assuming no anomalies in scans *not* assessed by radiologists), and we are circumspect in the interpretation of our findings. Because our study relies on a small number of cases – three only – we do not claim that any causal link exists between synesthesia and MS-RIS, and we present our findings with this strong caveat. Nonetheless, we present these significant data so that imaging researchers might consider them when evaluating any anomalies that may arise in future studies. If our epidemiological findings are indeed later supported by additional evidence, this could invite a debate about the clinical status of synesthesia, which has previously been associated with largely beneficial rather than unfavorable characteristics (but see Carruthers, Miller, Tarrier, & Whorwell, 2012). To investigate this hypothesis further, we are currently also exploring whether developmental synesthesia is found in high numbers within populations of people with MS, which would enable firmer conclusions to be drawn regarding the validity or otherwise of the statistical associations we report here.

Acknowledgments

We are grateful to Daisy Mollison for her radiological expertise, to Richard Shillcock for his feedback on the manuscript, to Linda Williams (Centre for Population and Health Sciences) for her epidemiological and statistical guidance, and to Catherine Oppenheim and Lucie Hertz-Pannier for their help retrieving archived data. The authors declare no competing interests.

Funding

DAC was supported in part by grants [grant number EP/F500385/1], [grant number BB/F529254/1] for the University of Edinburgh, School of Informatics Doctoral Training Centre in Neuroinformatics and Computational Neuroscience (www.anc.ac.uk/dtc) from the UK Engineering and Physical Sciences Research Council (EPSRC), UK Biotechnology and Biological Sciences Research Council (BBSRC), and the UK Medical Research Council (MRC).

Notes

1. Where MS-RIS anomalies were found, authorship was invited for the current article and this would explain why three cases were found in our own cohort but not elsewhere.
2. Calculation of the rate of female MS in Europeans: Pugliatti et al. (2006) report that "the total estimated prevalence rate of MS [in Europe] for the past three decades is 83 per 100 000 with … a female: male ratio around 2.0" (p. 700). On this basis, and given the overall population sex ratio in the European Union (0.96 males to each female; The World Factbook, 2011, Washington, DC: Central Intelligence Agency, 2011), we calculate the estimated European female MS rate at 110/100,000.
3. Calculation of the rate of female MS in England: There was no available data for female MS prevalence in England per se and so we calculated this based on the rate of MS in eastern England (153/100,000; the highest regional rate in England reported by Compston et al., 2006) and the male: female ratio of MS (2:1; Compston et al., 2006) in combination with the overall population prevalence of women versus men in the United Kingdom (1.01:1; The World Factbook, 2011, Washington, DC: Central Intelligence Agency, 2011). This gives an estimate of female MS in England at 204/100,000.
4. Analyzing the RIS cases and MS case separately serves an additional purpose. The MS case was the first reported case and as such can be viewed as the observation that led to the forming of our hypothesis. It could be argued that including this case in subsequent analyses, especially given the small numbers of cases involved, may lead to inappropriate conclusions being drawn. It is important to point out therefore that when this initial case is excluded and the subsequent two cases are analyzed, the outcome remains statistically significant, adding further methodological rigor for this hypothesis.

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